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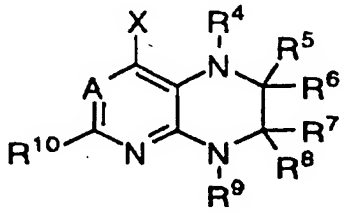
(54) Title: TETRAHYDROPTERIDINES AND PYRIDYLPIPERAZINES FOR TREATMENT OF NEUROLOGICAL DISORDERS

(57) Abstract

Corticotropin releasing factor (CRF) antagonists of formula (I) and their use in treating anxiety, depression, and other psychiatric and neurological disorders.



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TITLE

Tetrahydropteridines and Pyridylpiperazines for Treatment of Neurological Disorders

FIELD OF THE INVENTION

This invention relates to compounds and pharmaceutical compositions, and to methods of using same in the treatment of psychiatric disorders and neurological diseases including major depression, anxiety-related disorders, post-traumatic stress disorder, supranuclear palsy and feeding disorders.

BACKGROUND OF THE INVENTION

Corticotropin releasing factor (herein referred to as CRF), a 41 amino acid peptide, is the primary physiological regulator of proopiomelanocortin(POMC) -derived peptide secret.gland [J. Rivier et al., *Proc. Nat. Acad. Sci. (USA)* 80:4851 (**1983**); W. Vale et al., *Science* 213:1394 (**1981**)]. In addition to its endocrine role at the pituitary gland, immunohistochemical localization of CRF has demonstrated that the hormone has a broad extrahypothalamic distribution in the central nervous system and produces a wide spectrum of autonomic, electrophysiological and behavioral effects consistent with a neurotransmitter or neuromodulator role in brain [W. Vale et al., *Rec. Prog. Horm. Res.* 39:245 (**1983**); G.F. Koob, *Persp. Behav. Med.* 2:39 (**1985**); E.B. De Souza et al., *J. Neurosci.* 5:3189 (**1985**)]. There is also evidence that CRF plays a significant role in integrating the response of the immune system to physiological, psychological, and immunological stressors [J.E. Blalock, *Physiological Reviews* 69:1 (**1989**); J.E. Morley, *Life Sci.* 41:527 (**1987**)].

Clinical data provide evidence that CRF has a role in psychiatric disorders and neurological diseases including depression, anxiety-related disorders and feeding disorders. A role for CRF has also been postulated in the etiology and pathophysiology of Alzheimer's disease, Parkinson's disease, Huntington's disease, progressive supranuclear palsy and amyotrophic lateral sclerosis as they relate to the dysfunction of CRF neurons in the central nervous system [for review see E.B. De Souza, *Hosp. Practice* 23:59 (**1988**)].

In affective disorder, or major depression, the concentration of CRF is significantly increased in the cerebral spinal fluid (CSF) of drug-free individuals [C.B. Nemeroff et al., *Science* 226:1342 (**1984**); C.M. Banki et al., *Am. J. Psychiatry* 144:873 (**1987**); R.D. France et al., *Biol. Psychiatry* 28:86 (**1988**); M. Arato et al., *Biol Psychiatry* 25:355 (**1989**)]. Furthermore, the density of CRF receptors is significantly decreased in the frontal cortex of suicide victims, consistent with a hypersecretion of CRF [C.B. Nemeroff et al., *Arch. Gen. Psychiatry* 45:577 (**1988**)]. In addition, there is a blunted adrenocorticotropin (ACTH) response to CRF (i.v. administered) observed in depressed patients [P.W. Gold et al., *Am J. Psychiatry* 141:619 (**1984**); F. Holsboer et al., *Psychoneuroendocrinology* 9:147 (**1984**); P.W. Gold et al., *New Eng. J. Med.* 314:1129 (**1986**)]. Preclinical studies in rats and non-human primates provide additional support for the hypothesis that hypersecretion of CRF may be involved in the symptoms seen in human depression [R.M. Sapolsky, *Arch. Gen. Psychiatry* 46:1047 (**1989**)]. There is preliminary evidence that tricyclic antidepressants can alter CRF levels and thus modulate the numbers of CRF receptors in brain [Grigoriadis et al., *Neuropsychopharmacology* 2:53 (**1989**)].

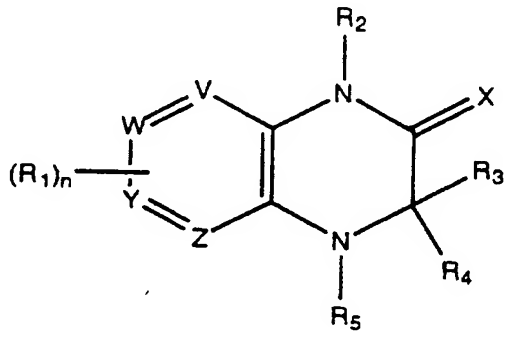
There has also been a role postulated for CRF in the etiology of anxiety-related disorders. CRF produces

anxiogenic effects in animals and interactions between benzodiazepine / non-benzodiazepine anxiolytics and CRF have been demonstrated in a variety of behavioral anxiety models [D.R. Britton et al., *Life Sci.* 31:363 (**1982**); C.W. Berridge and A.J. Dunn *Regul. Peptides* 16:83 (**1986**)]. Preliminary studies using the putative CRF receptor antagonist a-helical ovine CRF (9-41) in a variety of behavioral paradigms demonstrate that the antagonist produces "anxiolytic-like" effects that are qualitatively similar to the benzodiazepines [C.W. Berridge and A.J. Dunn *Horm. Behav.* 21:393 (**1987**), *Brain Research Reviews* 15:71 (**1990**)]. Neurochemical, endocrine and receptor binding studies have all demonstrated interactions between CRF and benzodiazepine anxiolytics providing further evidence for the involvement of CRF in these disorders. Chlordiazepoxide attenuates the "anxiogenic" effects of CRF in both the conflict test [K.T. Britton et al., *Psychopharmacology* 86:170 (**1985**); K.T. Britton et al., *Psychopharmacology* 94:306 (**1988**)] and in the acoustic startle test [N.R. Swerdlow et al., *Psychopharmacology* 88:147 (**1986**)] in rats. The benzodiazepine receptor antagonist (Ro15-1788), which was without behavioral activity alone in the operant conflict test, reversed the effects of CRF in a dose-dependent manner while the benzodiazepine inverse agonist (FG7142) enhanced the actions of CRF [K.T. Britton et al., *Psychopharmacology* 94:306 (**1988**)].

The mechanisms and sites of action through which the standard anxiolytics and antidepressants produce their therapeutic effects remain to be elucidated. It has been hypothesized however, that they are involved in the suppression of the CRF hypersecretion that is observed in these disorders. Of particular interest is that preliminary studies examining the effects of a CRF receptor antagonist (a-helical CRF9-41) in a variety of behavioral paradigms have demonstrated that the CRF

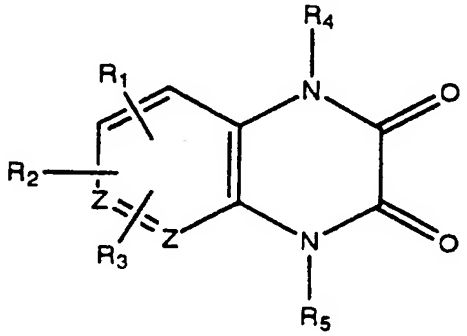
antagonist produces "anxiolytic-like" effects qualitatively similar to the benzodiazepines [for review see G.F. Koob and K.T. Britton, In: *Corticotropin-Releasing Factor: Basic and Clinical Studies of a Neuropeptide*, E.B. De Souza and C.B. Nemeroff eds., CRC Press p221 (1990)].

Several published patent applications disclose corticotropin releasing factor antagonist compounds. Among these are DuPont Merck PCT application US94/11050, Pfizer WO 95/33750, Pfizer WO 95/34563, and Pfizer WO 95/33727. U.S. Patent 5,424,311 discloses antiviral use of azaquinoxalines of the formula:



in which V, W, Y and Z are CH, CR1, or N; X can be oxygen, sulfur or NR^2; R^1 can be alkyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, or alkylamino; R^2, R^3, R^4 and R^5 can be hydrogen, alkyl, aryl or heteroaryl.

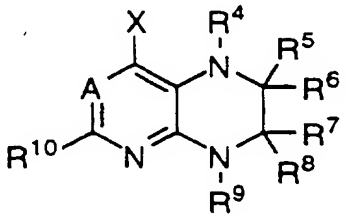
U.S. Patent 5,283,244 discloses glutamate receptor antagonizing activity of fused pyrazine derivatives of the the formula:



wherein Z represents C or N; R1 represents a diazole or triazole substituent; and the other R groups represent hydrogen or various substituents such as alkyl, phenyl, or heterocycle.

SUMMARY OF THE INVENTION

This invention is a method of treating an affective disorder, anxiety, depression, irritable bowel syndrome, post-traumatic stress disorder, supranuclear palsy, immune suppression, Alzheimer's disease, gastrointestinal disease, anorexia nervosa or other feeding disorder, drug or alcohol withdrawal symptoms, drug addiction, or inflammatory disorder in a mammal comprising administering to the mammal a therapeutically effective amount of a CRF antagonist compound of formula I:



(I)

or a pharmaceutically accetable salt or prodrug thereof, wherein:

A is N or C-R^{11};

X is H, OR^1, $S(O)_nR^1$, NR^1R^2, $CR^1R^2R^3$, phenyl (optionally substituted with 1-4 groups independently chosen from halogen, C_1-C_4 haloalkyl, nitro, C_1-C_4 alkyl, C_2-C_5 carboalkoxy, cyano, OH, C_1-C_4 alkoxy, SH, C_1-C_4 alkylthio, NH_2, C_1-C_4 alkylamino, C_2-C_8 dialkylamino, or phenyl) or heteroaryl (optionally substituted at one to all valence-allowed positions with groups independently chosen from halogen, C_1-C_4 haloalkyl, nitro, C_1-C_4 alkyl, C_2-C_5 carboalkoxy,

cyano, OH, C_1-C_4 alkoxy, SH, C_1-C_4 alkylthio, NH_2, C_1-C_4 alkylamino, C_2-C_8 dialkylamino, or phenyl);

n is 0, 1 or 2;

R^1 is C_1-C_{12} alkyl, C_2-C_{12} alkoxyalkyl, C_3-C_{12} cycloalkyl, C_4-C_{12} cycloalkylalkyl, C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, aryl-(C_1-C_{12} alkyl), C_3-C_{12} dialkylaminoalkyl, C_2-C_{13} cyanoalkyl, C_2-C_5 carboalkoxy-(C_1-C_{12} alkyl), phenyl (optionally substituted with 1-4 groups independently chosen from halogen, C_1-C_4 haloalkyl, nitro, C_1-C_4 alkyl, C_2-C_5 carboalkoxy, cyano, OH, C_1-C_4 alkoxy, SH, C_1-C_4 alkylthio, NH_2, C_1-C_4 alkylamino, C_2-C_8 dialkylamino, or phenyl), or heteroaryl (optionally substituted at one to all valence-allowed positions with groups independently chosen from halogen, C_1-C_4 haloalkyl, nitro, C_1-C_4 alkyl, C_2-C_5 carboalkoxy, cyano, OH, C_1-C_4 alkoxy, SH, C_1-C_4 alkylthio, NH_2, C_1-C_4 alkylamino, C_2-C_8 dialkylamino, or phenyl);

R^2 and R^3 are independently chosen from H, C_1-C_{12} alkyl, C_2-C_{12} alkoxyalkyl, C_3-C_{12} cycloalkyl, C_4-C_{12} cycloalkylalkyl, C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, aryl-(C_1-C_{12} alkyl), C_3-C_{12} dialkylaminoalkyl, C_2-C_{13} cyanoalkyl, C_1-C_4 carboalkoxy, C_2-C_{12} carboalkoxyalkyl, $C(=O)CH_3$, phenyl (optionally substituted with 1-4 groups independently chosen from halogen, C_1-C_4 haloalkyl, nitro, C_1-C_4 alkyl, C_2-C_5 carboalkoxy, cyano, OH, C_1-C_4 alkoxy, SH, C_1-C_4 alkylthio, NH_2, C_1-C_4 alkylamino, C_2-C_8 dialkylamino, or phenyl), or heteroaryl (optionally substituted at one to all valence-allowed positions with groups independently chosen from halogen, C_1-C_4 haloalkyl, nitro, C_1-C_4 alkyl, C_2-C_5 carboalkoxy, cyano, OH, C_1-C_4 alkoxy, SH, C_1-C_4 alkylthio, NH_2, C_1-C_4 alkylamino, C_2-C_8 dialkylamino, or phenyl);

R^4 is H, C_1-C_{12} alkyl, allyl, propargyl or benzyl (optionally substituted with 1-4 groups independently chosen from halogen, C_1-C_4 haloalkyl,

nitro, C_1-C_4 alkyl, C_2-C_5 carboalkoxy, cyano, OH, C_1-C_4 alkoxy, SH, C_1-C_4 alkylthio, NH_2, C_1-C_4 alkylamino, C_2-C_8 dialkylamino, or phenyl);

R^1 and R^4 may also optionally be taken together, along with the other four interconnected atoms, to form a ring of 5-9 total atoms, the structural sequence between the X group and the ring nitrogen atom consisting of the group $(CH_2)_pW(CH_2)_q$;

p and q are independently 0, 1 or 2;

W is CH_2, $C(CH_3)_2$, C(=O), O, S or NCH_3;

R^5, R^6, R^7 and R^8 are independently chosen from H, C_1-C_4 alkyl, allyl, propargyl, phenyl (optionally substituted with 1-4 groups independently chosen from halogen, C_1-C_4 haloalkyl, nitro, C_1-C_4 alkyl, C_2-C_5 carboalkoxy, cyano, OH, C_1-C_4 alkoxy, SH, C_1-C_4 alkylthio, NH_2, C_1-C_4 alkylamino, C_2-C_8 dialkylamino, or phenyl) or benzyl (optionally substituted with 1-4 groups independently chosen from halogen, C_1-C_4 haloalkyl, nitro, C_1-C_4 alkyl, C_2-C_5 carboalkoxy, cyano, OH, C_1-C_4 alkoxy, SH, C_1-C_4 alkylthio, NH_2, C_1-C_4 alkylamino, C_2-C_8 dialkylamino, or phenyl);

R^4, R^5 and R^6 may also be taken together, along with the two interconnecting atoms, to constitute either an imidazole or tetrazole ring, the imidazole ring being optionally substituted with 1-2 groups chosen independently from C_1-C_4 alkyl or phenyl;

R^5 and R^6 may also be taken together to be O, S or NR^{12};

R^9 is phenyl (optionally substituted with 1-4 groups chosen from halogen, C_1-C_4 haloalkyl, C_1-C_4 alkyl, C_2-C_6 alkenyl, C_1-C_4 alkoxy, C_1-C_4 alkylthio, C_1-C_4 alkylsulfonyl, C_2-C_6 dialkylamino, nitro, C_2-C_5 carboalkoxy or cyano), pyridyl (optionally substituted with 1-4 groups chosen from halogen,

C_1-C_4 haloalkyl, C_1-C_4 alkyl, C_2-C_6 alkenyl, C_1-C_4 alkoxy, C_1-C_4 alkylthio, C_1-C_4 alkylsulfonyl, C_2-C_6 dialkylamino, nitro, C_2-C_5 carboalkoxy or cyano), or pyrimidyl (optionally substituted with 1-4 groups chosen from halogen, C_1-C_4 haloalkyl, C_1-C_4 alkyl, C_2-C_6 alkenyl, C_1-C_4 alkoxy, C_1-C_4 alkylthio, C_1-C_4 alkylsulfonyl, C_2-C_6 dialkylamino, nitro, C_2-C_5 carboalkoxy or cyano);

R^{10} is H, C_1-C_4 alkyl or cyano;

R^{11} is H, C_1-C_4 alkyl or halogen;

R^{12} is H, C_1-C_4 alkyl or phenyl;

aryl is phenyl, biphenyl or naphthyl; and

heteroaryl is pyridyl, pyrimidinyl, triazinyl, furanyl, quinolinyl, isoquinolinyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrrolyl, oxazolyl, benzofuranyl, benzothienyl, benzthiazolyl, isoxazolyl or pyrazolyl.

Compounds of formula I, other than those in which R5 and R6 are taken together and are O, S or NR12, are novel. This invention includes the novel compounds of formula I and pharmaceutical compositions containing them.

Preferred compounds for use in the method of this invention are compounds of formula (I) wherein:

X is OR^1, NR^1R^2, $CR^1R^2R^3$, or phenyl (optionally substituted at the 2-position with CF_3, nitro, halogen or cyano);

R^1 is C_1-C_{12} alkyl , C_2-C_{12} alkoxyalkyl, C_3-C_{12} cycloalkyl, C_4-C_{12} cycloalkylalkyl, aryl-(C_1-C_{12} alkyl), C_3-C_{12} dialkylaminoalkyl, or phenyl (optionally substituted with 1-4 groups independently chosen from halogen, haloalkyl, nitro, C_1-C_4 alkyl, C_2-C_5 carboalkoxy, cyano, OH,

C_1-C_4 alkoxy, SH, C_1-C_4 alkylthio, NH_2, C_1-C_4 alkylamino, C_2-C_8 dialkylamino, or phenyl);

R^4 is H or C_1-C_4 alkyl;

R^5 and R^6 are either H or C_1-C_4 alkyl;

R^4, R^5 and R^6 may also be taken together, along with the two interconnecting atoms, to constitute a tetrazole ring;

R^9 is phenyl (optionally substituted with 1-4 groups chosen from halogen, C_1-C_4 haloalkyl, C_1-C_4 alkyl, C_2-C_6 alkenyl, C_1-C_4 alkoxy, C_1-C_4 alkylthio, C_1-C_4 alkylsulfonyl, C_2-C_6 dialkylamino, nitro, C_2-C_5 carboalkoxy or cyano), 3-pyridyl (optionally substituted with 1-4 groups chosen from halogen, C_1-C_4 haloalkyl, C_1-C_4 alkyl, C_2-C_6 alkenyl, C_1-C_4 alkoxy, C_1-C_4 alkylthio, C_1-C_4 alkylsulfonyl, C_2-C_6 dialkylamino, nitro, C_2-C_5 carboalkoxy or cyano), or 5-pyrimidyl (optionally substituted with 1-4 groups chosen from halogen, C_1-C_4 haloalkyl, C_1-C_4 alkyl, C_2-C_6 alkenyl, C_1-C_4 alkoxy, C_1-C_4 alkylthio, C_1-C_4 alkylsulfonyl, C_2-C_6 dialkylamino, nitro, C_2-C_5 carboalkoxy or cyano);

R^{10} is CH_3;

and R^{11} is H.

More preferred compounds in this invention are of the formula (I) wherein:

A is N;

X is NR^1R^2 or $CR^1R^2R^3$;

R^1 is C_1-C_6 alkyl or C_2-C_8 alkoxyalkyl;

R^2 and R^3 are independently H, C_1-C_6 alkyl or C_2-C_8 alkoxyalkyl;

R^4 is H;

R^5 and R^6 are H;

R^7 and R^8 are independently H or CH_3;

and R^9 is phenyl (optionally substituted with 1-4 groups

chosen from halogen, C_1-C_4 haloalkyl, C_1-C_4 alkyl, C_2-C_6 alkenyl, C_1-C_4 alkoxy, C_1-C_4 alkylthio, C_1-C_4 alkylsulfonyl, C_2-C_6 dialkylamino, nitro, C_2-C_5 carboalkoxy or cyano).

Specifically preferred because of their biological activity are the following compounds:

8-(2-bromo-4-isopropylphenyl)-4-(ethylbutylamino)-2-methyl-5,6,7,8-tetrahydropteridine;

8-(2-chloro-4,6-dimethoxyphenyl)-4-(ethylbutylamino)-2-methyl-5,6,7,8-tetrahydropteridine;

4-(ethylbutylamino)-2-methyl-8-(2,4,6-trimethylphenyl)-5,6,7,8-tetrahydropteridine;

and 4-(1-methoxy-2-butyl)amino-2-methyl-8-(2,4,6-trimethylphenyl)-5,6,7,8-tetrahydropteridine.

DETAILED DESCRIPTION OF THE INVENTION

Many compounds of this invention have one or more asymmetric centers or planes. Unless otherwise indicated, all chiral (enantiomeric and diastereomeric) and racemic forms are included in the present invention. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds, and all such stable isomers are contemplated in the present invention. The compounds may be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of racemic forms or by synthesis from optically active starting materials. All chiral, (enantiomeric and diastereomeric) and racemic forms and all geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomer form is specifically indicated.

The term "alkyl" includes both branched and straight-chain alkyl having the specified number of carbon atoms. "Alkenyl" includes hydrocarbon chains of

either a straight or branched configuration and one or more unsaturated carbon-carbon bonds which may occur in any stable point along the chain, such as ethenyl, propenyl, and the like. "Alkynyl" includes hydrocarbon chains of either a straight or branched configuration and one or more triple carbon-carbon bonds which may occur in any stable point along the chain, such as ethynyl, propynyl and the like. "Haloalkyl" is intended to include both branched and straight-chain alkyl having the specified number of carbon atoms, substituted with 1 or more halogen; "alkoxy" represents an alkyl group of indicated number of carbon atoms attached through an oxygen bridge; "cycloalkyl" is intended to include saturated ring groups, including mono-,bi- or poly-cyclic ring systems, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and so forth. "Halo" or "halogen" includes fluoro, chloro, bromo, and iodo.

The term "substituted", as used herein, means that one or more hydrogen on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency is not exceeded, and that the substitution results in a stable compound. When a substitent is keto (i.e., =O), then 2 hydrogens on the atom are replaced.

Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. By "stable compound" or "stable structure" is meant a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

The term "appropriate amino acid protecting group" means any group known in the art of organic synthesis for the protection of amine or carboxylic acid groups. Such amine protecting groups include those listed in Greene and Wuts, "Protective Groups in Organic Synthesis" John Wiley & Sons, New York (1991) and "The

Peptides: Analysis, Synthesis, Biology, Vol. 3, Academic Press, New York (1981), the disclosure of which is hereby incorporated by reference. Any amine protecting group known in the art can be used. Examples of amine protecting groups include, but are not limited to, the following: 1) acyl types such as formyl, trifluoroacetyl, phthalyl, and p-toluenesulfonyl; 2) aromatic carbamate types such as benzyloxycarbonyl (Cbz) and substituted benzyloxycarbonyls, 1-(p-biphenyl)-1-methylethoxycarbonyl, and 9-fluorenylmethyloxycarbonyl (Fmoc); 3) aliphatic carbamate types such as tert-butyloxycarbonyl (Boc), ethoxycarbonyl, diisopropylmethoxycarbonyl, and allyloxycarbonyl; 4) cyclic alkyl carbamate types such as cyclopentyloxycarbonyl and adamantyloxycarbonyl; 5) alkyl types such as triphenylmethyl and benzyl; 6) trialkylsilane such as trimethylsilane; and 7) thiol containing types such as phenylthiocarbonyl and dithiasuccinoyl.

The term "amino acid" as used herein means an organic compound containing both a basic amino group and an acidic carboxyl group. Included within this term are natural amino acids, modified and unusual amino acids, as well as amino acids which are known to occur biologically in free or combined form but usually do not occur in proteins. Included within this term are modified and unusual amino acids, such as those disclosed in, for example, Roberts and Vellaccio (1983) The Peptides, 5: 342-429, the teaching of which is hereby incorporated by reference. Modified or unusual amino acids which can be used to practice the invention include, but are not limited to, D-amino acids, hydroxylysine, 4-hydroxyproline, an N-Cbz-protected amino acid, ornithine, 2,4-diaminobutyric acid, homoarginine, norleucine, N-methylaminobutyric acid, naphthylalanine, phenylglycine, ß-phenylproline, tert-leucine, 4-aminocyclohexylalanine, N-methyl-

norleucine, 3,4-dehydroproline, N,N-dimethylaminoglycine, N-methylaminoglycine, 4-aminopiperidine-4-carboxylic acid, 6-aminocaproic acid, trans-4-(aminomethyl)-cyclohexanecarboxylic acid, 2-, 3-, and 4-(aminomethyl)-benzoic acid, 1-aminocyclopentanecarboxylic acid, 1-aminocyclopropanecarboxylic acid, and 2-benzyl-5-aminopentanoic acid.

The term "amino acid residue" as used herein means that portion of an amino acid (as defined herein) that is present in a peptide.

The term "peptide" as used herein means a compound that consists of two or more amino acids (as defined herein) that are linked by means of a peptide bond. The term "peptide" also includes compounds containing both peptide and non-peptide components, such as pseudopeptide or peptide mimetic residues or other non-amino acid components. Such a compound containing both peptide and non-peptide components may also be referred to as a "peptide analog".

The term "peptide bond" means a covalent amide linkage formed by loss of a molecule of water between the carboxyl group of one amino acid and the amino group of a second amino acid.

The term "pharmaceutically acceptable salts" includes acid or base salts of the compounds of formulas (I) and (II). Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like.

Pharmaceutically acceptable salts of the compounds of the invention can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl

acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, PA, 1985, p. 1418, the disclosure of which is hereby incorporated by reference.

"Prodrugs" are considered to be any covalently bonded carriers which release the active parent drug of formula (I) or (II) *in vivo* when such prodrug is administered to a mammalian subject. Prodrugs of the compounds of formula (I) and (II) are prepared by modifying functional groups present in the compounds in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent compounds. Prodrugs include compounds wherein hydroxy, amine, or sulfhydryl groups are bonded to any group that, when administered to a mammalian subject, cleaves to form a free hydroxyl, amino, or sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol and amine functional groups in the compounds of formulas (I) and (II); and the like.

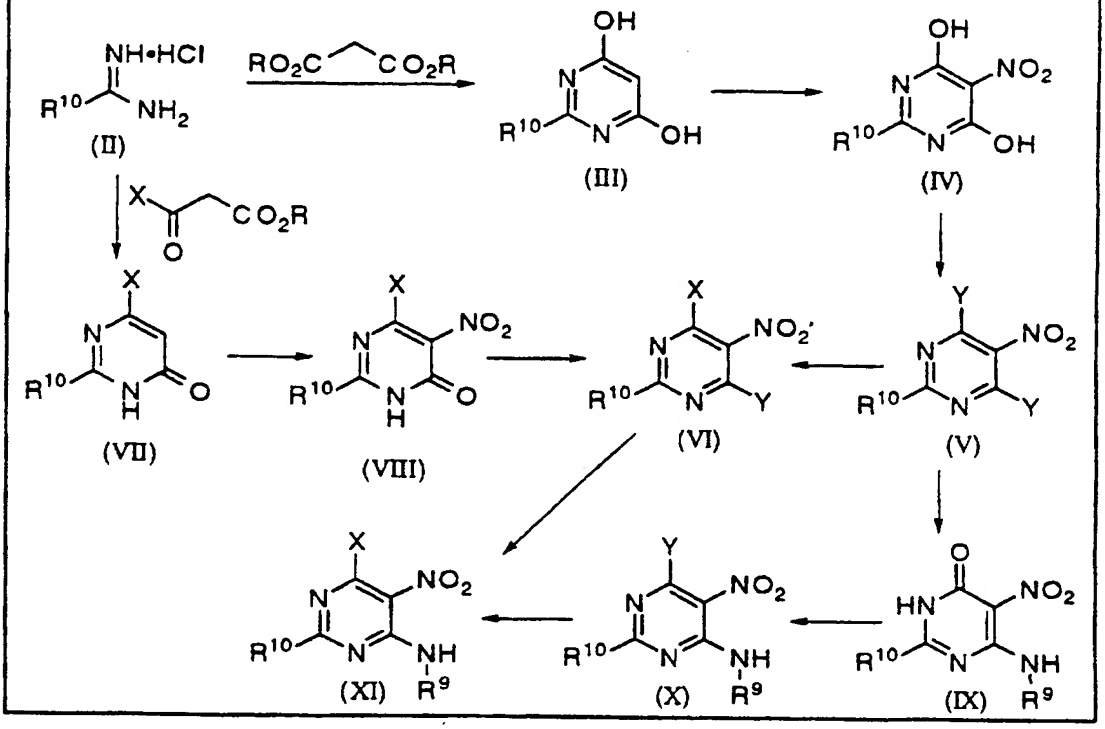
The term "therapeutically effective amount" of a compound of this invention means an amount effective to antagonize abnormal level of CRF or treat the symptoms of affective disorder, anxiety or depression in a host.

Synthesis

Synthesis of compounds of Formula (I) wherein A = N may begin with amidine compounds of Formula (II) (Scheme I), which are available commercially or synthetically from heating a nitrile compound and an ammonium salt. Compound (II) may then be condensed with a malonate ester (using conditions such as sodium in ethanol) to give a dihydroxy-pyrimidine compound of Formula (III). Nitration at the 5-position may be accomplished through the use of such conditions as concentrated nitric acid

with or without the presence of another acid such as concentrated sulfuric or glacial acetic. The hydroxy groups of the nitrated compound of Formula (IV) may then be converted into leaving groups (Y), which include chloro, bromo, toluenesulfonate, or methanesulfonate. The dichloro compound (Formula (V), Y = Cl) may be prepared from the dihydroxy by a reagent such as phosphorus oxychloride, with or without the assistance of a catalyst such as diethylaniline. The bis(toluenesulfonate) compound (Formula (V), Y = $OSO_2C_6H_4CH_3$), may be prepared from the dihydroxy compound by treatment with a reagent such as toluenesulfonic anhydride. Careful addition one equivalent of a suitable form of a compound X-H to the compound of Formula (V) results in replacement of one of the Y groups with X. This is of particular utility when the X group represents a nucleophilic atom, such as nitrogen, sulfur or oxygen. Conditions which will facilitate this transformation include the optional presence of bases such as sodium hydride, triethylamine, diisopropylethylamine or

Scheme I



potassium carbonate, in solvents such as tetrahydrofuran, dimethylformamide, dimethylsulfoxide, methylene chloride, acetonitrile or ethanol, at appropriate temperatures.

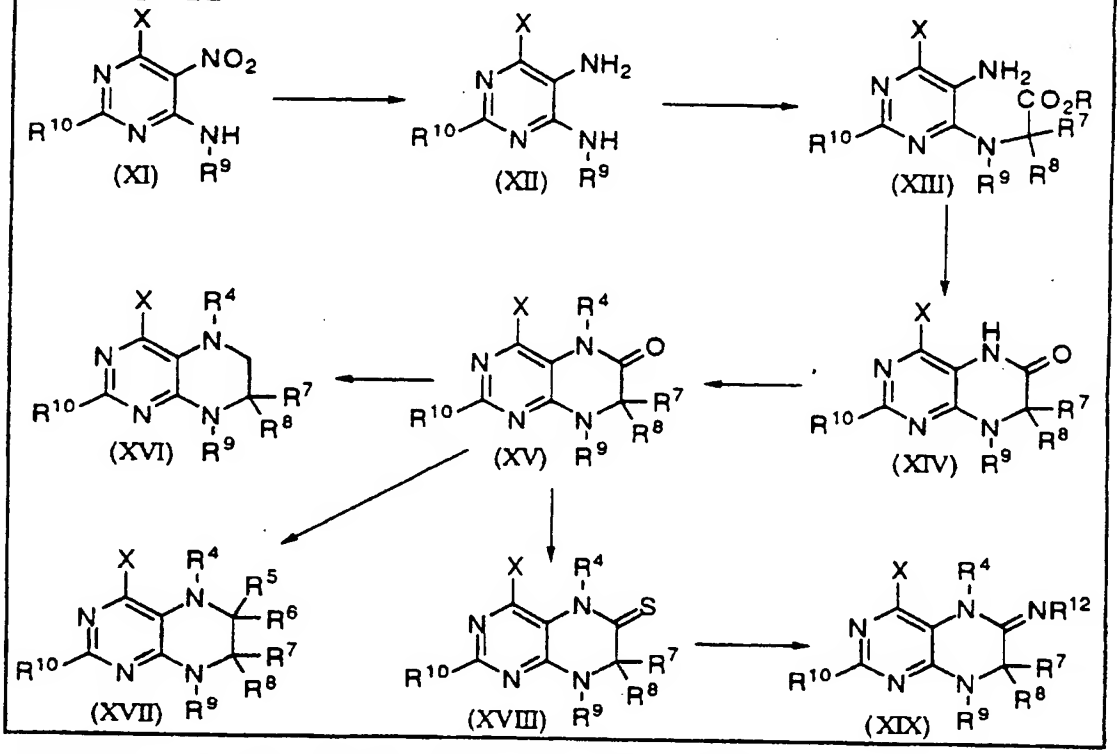
Alternatively, in the case where X represents a group without a corresponding nucleophilic compound X-H being available, one may condense a compound of Formula (II) with an appropriately-substituted ketoester (using conditions similar to those for the malonate condensation) to obtain a compound of Formula (VII). Nitration conditions similar to those described above may then be used to prepare the nitro compound (VIII). Conversion of the pyrimidone group to the desired Y group may then be accomplished using the same conditions as described above for the transformation of (IV) to (V).

A third alternative involves treatment of the compound of Formula (V) with a compound R^9-NH_2. Conditions may be found for each Y group so that one Y group is replaced by R^9-NH, and the other is hydrolyzed to the pyrimidone (compound Formula (IX)). For example, for Y = Cl, this conversion may be effected by slow addition of a dimethylsulfoxide solution of one equivalent of R^9-NH_2 to a dimethylsulfoxide solution of compound (V), followed by aqueous workup. The pyrimidione of Formula (IX) may be converted to Y-bearing compound (Formula (X)) using the conditions described above for (IV) to (V). The Y group can then be replaced with X analogously to the transformation of (V) to (VI) to give a compound of Formula (XI).

Alternatively, the compound of Formula (VI) may be converted to the compound of Formula (XI) by treatment with the compound R^9-NH_2. Suitable conditions for this reaction include treatment with excess sodium hydride in refluxing toluene or heating the two compounds together in an alcoholic solvent (ethanol, propanol, butanol, ethylene glycol, ethoxyethoxyethanol) or other polar, aprotic solvents (such as dimethylformamide, 1,4-dioxane, dimethoxyethane or diglyme) without a base to effect the coupling.

Scheme II shows the appending of the second ring onto the pyrimidine ring. The nitro group in the compound of Formula (XI) can be reduced to an amino group using conditions such as sodium dithionite, catalytic hydrogenation, iron or zinc. The compound of Formula (XII) may be treated with a base such as sodium hydride (in solvents such as dimethylformamide, dimethyl sulfoxide, 1,4-dioxane, tetrahydrofuran, etc.), followed by a reagent of the general formula Y-CR^7R^8-CO_2R, where Y is halogen or psuedohalogen, and the structure of R is only important if

Scheme II



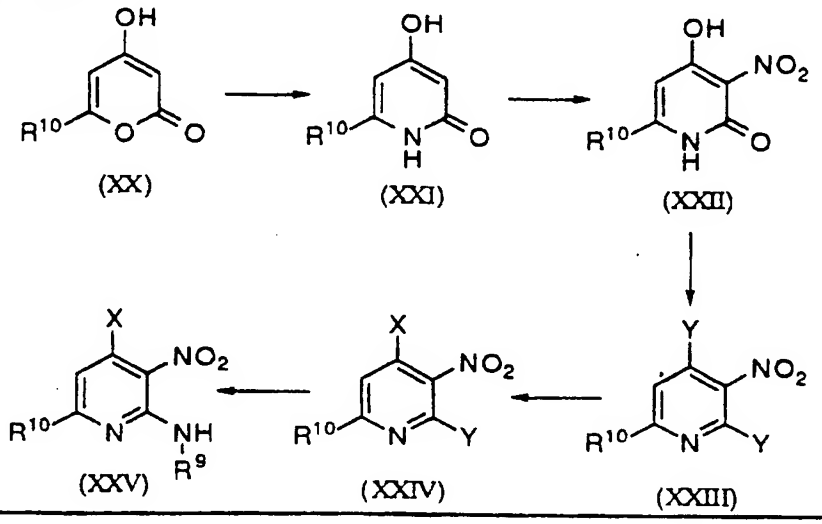
removal of the group prior to cyclization is desired. Cyclization of the compound of Formula (XIV) may be accomplished by heating in a solvent such as ethanol, dimethylformamide, etc. at temperatures ranging anywhere from ambient to the boiling point of the solvent. An additive such as an acid source (such as toluenesulfonic acid, aqueous hydrochloric, etc.), a base (triethylamine, sodium hydroxide, etc.) or a physical catalyst (such as molecular sieves) may be added, in quantities ranging from catalytic to stoichiometric to excess. In practice, the cyclization of (XIII) often is very facile, particularly in the case where R is lower alkyl, and will occur spontaneously in the reaction medium of the alkylation of compound (XII). Cyclized compound (XIV) may be alkylated with the R^4 group by first treatment with a base such as sodium hydride in a solvent such as dimethylformamide or dimethylsulfoxide, then an alkylating reagent (such as a halogen- or psuedohalogen-bearing compound) which provides the R^4

group, to provide the compound of Formula (XV). At this point, compounds derived from bromoacetate alkylation of compound (XII) can be alkylated with appropriate R^7 and R^8 by treatment with a strong base such as sodium hydride, lithium diisopropylamide or sodium hexamethyldisilazide, and then alkylating agents bearing the R^7 or R^8 groups, thus resulting in the compound of Formula (XV).

Compound (XV) is a key intermediate which may be used to generate variations of Formula (I). For example, the carbonyl group of compound (XV) may be reduced with reagents such as lithium aluminum hydride, borane (complexed with tetrahydrofuran or other suitable ligands) or diisobutylaluminum hydride, which will generate a compound of Formula (XVI). The carbonyl group may be substituted with R^5 and R^6 groups using appropriately-substituted organolithium or organomagnesium reagents, to prepare compounds of Formula (XVII). The carbonyl group of compound (XV) may be converted to thiocarbonyl by treatment with reagents such as Lawesson's Reagent or phosphorus pentasulfide in appropriate solvents (toluene, benzene, etc.). The thioamide group of compound (XVIII) may be converted to amidine using the method of Robba et al. (*Tetrahedron Letters* **1992**, *33*, 2803-2804), which involves treatment with an amine of formula R^{11}-NH_2 and a catalyst such as a mercury (II) salt. This will result in the synthesis of a compound of Formula (XIX).

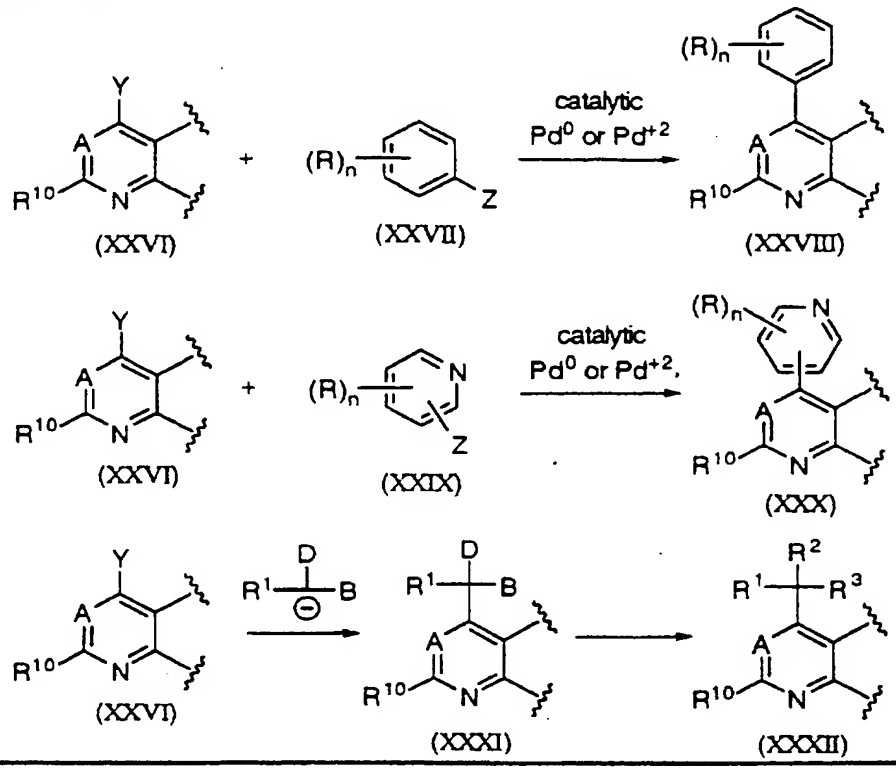
Compounds of Formula (I) composed of a fused pyridine ring (A = CH) may be prepared using very similar technology to that presented in Scheme II. In this case, however, the starting material is not of the structure (XI), but rather

Scheme III



of structural formula (XXV) (Scheme III). This compound may be prepared starting with a lactone compound of Formula (XX), which are available by dimerization of a ketoester $R^{10}C(=O)CH_2CO_2Et$ according to the method of Arndt (*Org. Syn., Coll. Vol. III*, p. 231), followed by deacylation according to the method of Collie et al. (*J. Chem. Soc.* **1907**, *91*, p. 787 and references therein). The ring oxygen atom may be replaced with nitrogen by treatment with conc. aq. ammonium hydroxide, according to the method of Wang (*J. Heterocyclic Chem.* **1970**, *1*, 389-392). Compound (XXI) may be nitrated similarly to the transformation of compound (III) to give compound (XXII). The hydroxy groups of compound (XXII) may be converted to leaving groups Y using the techniques discussed above for the conversion of compound (IV) to (V). The C^4 Y group may be selectively replaced with a nucleophilic X group, and the other Y group in compound (XXIV) may be replaced with NHR^9 by treatment with a compound R^9NH_2, either with no solvent or an appropriate solvent (such as a high-boiling alcohol) at temperatures sufficiently elevated to effect coupling. Compound (XXV)

Scheme IV



may then be employed in the same general way as for compound (XI) to generate compounds of Formula (I).

Further functionalization of this class of compounds may be achieved using a compound of Formula (XXVI) (Scheme IV), which represents some pyridine or pyridine compound (either uncyclized, like compounds (XI) or (XXV), or a cyclized compound) bearing a leaving group Y. The Y group may be replaced with phenyl or pyridyl using coupling reactions employing a phenyl (or pyridyl) compound of Formula (XXVII) (or (XXIX)) and an appropriate palladium catalyst. For example, arylboronic acids (Z = $B(OH)_2$) may be coupled to a heterocyclic halide using catalytic amounts of tetrakis(triphenylphosphine)palladium, which is the method of Suzuki, et al. (*Synthetic Communications* **1981**, *11*, p. 513-519). Other appropriate reagents for this coupling reaction includes organomagnesium (Z = MgBr or MgCl) reagents (with nickel (II) chloride

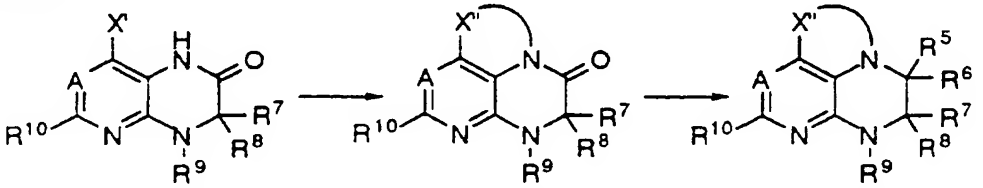
catalysis according to the method of Sugimori et al., *Synthetic Communications* **1991**, *21*, p. 481-487) or organozinc (Z = ZnCl) reagents (according to the method of Negishi et al., *J. Org. Chem.* **1977**, *42*, p. 1821-1823).

Other carbon substituents may be introduced into compound (XXVI) by treatment with a sodium salt (generated by the use of a base such as sodium ethoxide or sodium hydride) of an active methylene or methine reagent (i.e. where B and D are groups which stabilize adjacent anions, such as keto, carboalkoxy, cyano, alkyl- or aryl-sulfonyl, etc.). The resulting compounds of Formula (XXXI) may be further modified by conversion of the B and D groups into R^2 and R^3 groups. Those skilled in the art of organic synthesis should readily understand possible variations of these conversions to prepare a number of different R^1, R^2 and R^3 group substituents.

Preparation of compounds of Formula (I) wherein the R^1 and R^4 groups are taken together to form a ring may be accomplished beginning from a compound of Formula (XXXIII) (Scheme V), where X' is meant to designate a group NHR^2, OH, SH or CHR^2R^3. This compound may be treated with a base (such as sodium hydride) in an appropriate solvent, followed by a reagent bearing reactive terminii on both ends (for example, a dihaloalkane, a haloester, etc.). The X' and amide NH groups will couple with such a reagent under these conditions to form the third ring of compound (XXXIV). The amide group may then be modified as described above to give then final product of Formula (XXXV).

Compounds of Formula (I) wherein the R^4, R^5 and R^6 groups are taken together to form a heteroaromatic ring may

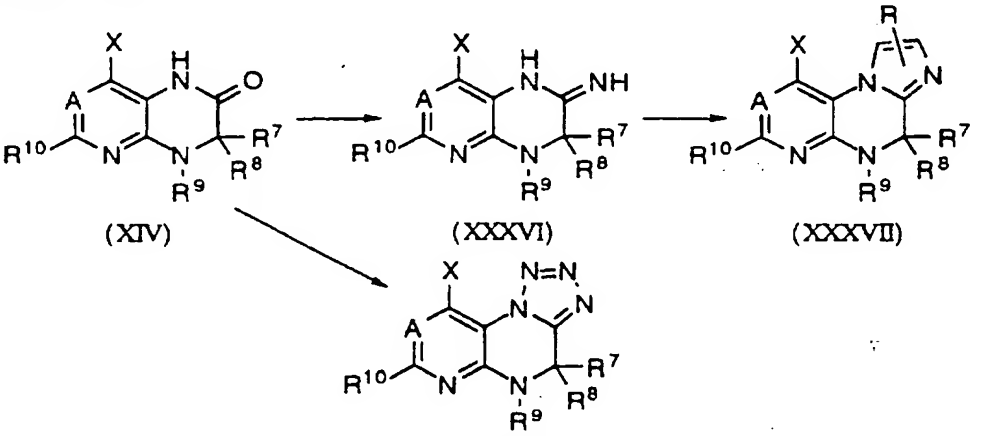
Scheme V



(XXXIII) (XXXIV) (XXXV)

be prepared using the strategy displayed in Scheme VI. Compound (XIV) may be converted to amidine (XXXVI), using the conditions described above for the preparation of compound (XIX). The amidine is treated with an α-halo- or α-hydroxyketone, under conditions such as refluxing alcohol, to afford the imidazole compound (XXXVII). Compound (XIV) may be converted to fused tetrazole compound (XXXVIII) using the conditions of Duncia et al. (*J. Org. Chem.* **1991**, *56*, p. 2395).

Scheme VI



(XIV) (XXXVI) (XXXVII)

(XXXVIII)

The experimental methods listed below for Examples 1, 17, 24, 42, 131, 143, 155, and 248 may be used in the preparation of all the compounds shown in Tables I (pyrimidines) and II (pyridines).

Example 1

Preparation of 8-(2-bromo-4-isopropylphenyl)-4-(ethylbutylamino)-2-methyl-5,6,7,8-tetrahydropteridin-6-one

Part A. A solution of 4,6-dichloro-2-methyl-5-nitropyrimidine (prepared using the methods of Albert, et al., *J. Chem. Soc.* **1954**, p. 3832) (2.77 g, 13.3 mmol) in absolute ethanol (25 mL) was cooled to 0 °C, and treated with triethylamine (2.00 mL, 14.3 mmol). Then, a solution of ethylbutylamine (1.80 mL, 13.2 mmol) in ethanol (3 mL) was added dropwise with stirring. The mixture was allowed to stir and warm to ambient temperature overnight, then was partitioned between water and ethyl acetate (100 mL each). The organic phase was seperated, washed with satd. aq. brine (100 mL), dried over anhydrous sodium sulfate, filtered and evaporated. The residue was separated by column chromatography (silica gel, dichloromethane) to afford 4-chloro-6-(ethylbutylamino)-2-methyl-5-nitropyrimidine as an oil (3.34 g, 12.2 mmol, 92%). Spectral data: TLC R_F 0.59 (dichloromethane). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.45 (2H, q, J = 7.0 Hz), 3.38 (2H, t, J = 7.7 Hz), 2.50 (3H, s), 1.62-1.52 (2H, m), 1.38-1.26 (2H, m), 1.20 (3H, t, J = 7.0 Hz), 0.94 (3H, t, J = 7.3 Hz). MS (NH_3-CI): *m/e* 276 (4), 275 (40), 274 (16), 273 (100).

Part B. The product of Part A above (2.97 g, 10.9 mmol) was dissolved in ethoxyethoxyethanol solution (11 mL), and treated with 2-bromo-4-isopropylaniline (2.34 g, 10.9 mmol). The mixture was heated to 120 °C for 4 h, then cooled and partitioned between water and ethyl acetate (100 mL each). The organic layer was separated and washed with two additional portions of water (100 mL

each) and brine (100 mL). The aqueous phases were all back-extracted in sequence with more ethyl acetate (100 mL). The extracts were combined, dried over sodium sulfate, filtered and evaporated. The residue was separated by column chromatography (silica gel, 5:95 ethyl acetate-hexane) to afford 6-(2-bromo-4-isopropylphenylamino)-4-(ethylbutylamino)-2-methyl-5-nitropyrimidine as an oil (3.05 g, 6.77 mmol, 62%). Spectral data: TLC R_F 0.56 (20:80 ethyl acetate-hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.30 (1H, br s), 8.32 (1H, d, J = 8.4 Hz), 7.45 (1H, d, J = 1.8 Hz), 7.19 (1H, dd, J = 8.4, 1.8 Hz), 3.52-3.42 (4H, m), 2.88 (1H, heptet, J = 7.0 Hz), 2.40 (3H, s), 1.70-1.58 (2H, m), 1.39-1.29 (2H, m), 1.26 (3H, t, obscurred), 1.25 (6H, d, J = 7.0 Hz), 0.94 (3H, t, J = 7.1 Hz). MS (NH_3-CI): *m/e* 454 (4), 453 (24), 452 (100), 451 (26), 450 (99).

Part C. The product of Part B above (256 mg, 568 µmol) was dissolved in 1:1 dioxane-water (3 mL), and treated with conc. aq. ammonium hydroxide (0.5 mL). To this was added, with stirring, solid sodium dithionite (440 mg, 2.53 µmol) in 3 portions over 1 h. The resulting solution was allowed to stir for an additional 8 h, then partitioned between water and ethyl acetate (100 mL). The organic layer was washed with brine, dried over sodium sulfate, filtered and evaporated. The residual material was purified by elution through a short plug of silica gel (20:80 ethyl acetate-hexane), and evaporation gave pure 5-amino-6-(2-bromo-4-isopropylphenylamino)-4-(ethylbutylamino)-2-methylpyrimidine as an oil (198 mg, 472 µmol, 83%). Spectral data: TLC R_F 0.26 (10:90 ethyl acetate-hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.15 (1H, d, J = 8.4 Hz), 7.38 (1H, d, J = 2.2 Hz), 7.15 (1H, dd, J = 8.4, 2.2 Hz), 7.04 (1H, br s), 3.30-3.19 (4H, m), 3.08 (2H, br s), 2.85 (1H, heptet, J = 7.0 Hz), 2.47 (3H, s), 1.57-1.44 (2H, m), 1.39-1.26 (2H, m), 1.23 (6H, d, J = 7.0 Hz), 1.11 (3H, t, J = 7.0 Hz), 0.91 (3H, t, J = 7.1 Hz). MS

(NH_3-CI): *m/e* 424 (3), 423 (24), 422 (100), 421 (26), 420 (100).

Part D. Sodium hydride dispersion in mineral oil (0.26 g w/w, 5.42 mmol) was washed with hexane, and the hexane was decanted off. The remaining solid was dried under vacuum and suspended in anhydrous dimethylformamide (5 mL). The resulting suspension was cooled in an ice bath, while the product of Part C above (1.78 g, 4.23 mmol) in dimethylfomamide solution (5 mL) was added slowly by syringe. After hydrogen evolution was complete, the mixture was treated slowly with ethyl bromoacetate (0.47 mL, 4.24 mmol) by syringe, and the mixture was allowed to stir for 10 h. It was partitioned between water and ethyl acetate (100 mL each), and the organic phase was washed with two additional portions of water (100 mL each) and brine (100 mL). The aqueous phases were back-extracted in sequence with ethyl acetate (100 mL), and the extracts were combined, dried over sodium sulfate, filtered and evaporated. The residue was separated by column chromatography (silica gel, 10:90 ethyl acetate-hexane) to afford the title product as a solid (1.35 g, 2.93 mmol, 69%). Spectral data: m.p. 146-147 °C. TLC R_F 0.49 (50:50 ethyl acetate-hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.53 (1H, s), 7.36 (1H, br s), 7.25 (2H, s), 4.44 (1H, d, J = 15 Hz), 4.25 (1H, d, J = 15 Hz), 3.29-3.15 (4H, m), 2.94 (1H, heptet, J = 7.0 Hz), 2.29 (3H, s), 1.54-1.45 (2H, m), 1.39-1.29 (2H, m), 1.28 (6H, d, J = 7.0 Hz), 1.11 (3H, t, J = 7.1 Hz), 0.92 (3H, t, J = 7.1 Hz). MS (NH_3-CI): *m/e* 464 (3), 463 (24), 462 (100), 461 (26), 460 (99). Analysis calc'd for $C_{22}H_{30}BrN_5O$: C, 57.39; H, 6.58; N, 15.21; found: C, 56.74; H, 6.02; N, 14.41.

Examples 143 and 155

Preparation of 8-(2-bromo-4-isopropylphenyl)-2,5-dimethyl-4-(ethylbutylamino)-5,6,7,8-tetrahydropteridin-6-one and 8-(2-bromo-4-isopropylphenyl)-4-

(ethylbutylamino)-2,5,7-trimethyl-5,6,7,8-tetrahydropteridin-6-one

Part A. Sodium hydride suspension in mineral oil (200 mg of 50% w/w, 4.17 mmol) was washed with hexane, dried under vacuum and suspended in anhydrous dimethylformamide (5 mL). This suspension was cooled to 0 °C, while a solution of the compound of Example 1 (1.58 g, 3.43 mmol) in dimethylformamide (5 mL) was added slowly by syringe. The resulting mixture was allowed to stir for 1 h, then was treated with methyl iodide (0.30 mL, 4.82 mmol) by syringe. The mixture was allowed to stir overnight, then was partitioned between water and ethyl acetate (100 mL each). The organic phase was washed with two additional portions of water and one of brine solution. The aqueous fractions were back-extracted in sequence with more ethyl acetate, and the organic layers were combined, dried over sodium sulfate, filtered and evaporated. The residual oil was separated by column chromatography (silica gel, 10:90 ethyl acetate-hexane) to afford two fractions. The first compound off the column was the title compound of Example 155 (150 mg, 0.31 mmol, 9%): TLC R_F 0.29 (20:80 ethyl acetate-hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.50 (1H, d, J = 1.8 Hz), 7.33 (1H, d, J = 8.0 Hz), 7.21 (1H, dd, J = 8.0, 1.8 Hz), 4.23 (1H, q, J = 7.3 Hz), 3.22 (3H, s), 3.19 (4H, br), 2.92 (1H, heptet, J = 7.0 Hz), 2.30 (3H, s), 1.55 (2H, br), 1.43-1.00 (8H, br), 1.27 (6H, d, J = 7.0 Hz), 0.91 (3H, br t, J = 7 Hz). MS (NH_3-CI): *m/e* 492 (3), 491 (28), 490 (96), 489 (30), 488 (100). The second compound off the column was the title compound of Example 143 (1.30 g, 2.74 mmol, 80%): TLC R_F 0.22 (20:80 ethyl acetate-hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.48 (1H, s), 7.21 (2H, s), 4.19 (2H, br), 3.21 (3H, s), 3.18 (4H, v br), 2.91 (1H, heptet, J = 6.6 Hz), 2.30 (3H, s), 1.55-1.46 (2H, m), 1.35-1.25 (2H, m), 1.27 (6H, d, J = 6.6 Hz), 1.11 (3H, br t, J = 7.0 Hz),

0.90 (3H, t, J = 7.0 Hz). MS (NH_3-CI): *m/e* 478 (3), 477 (28), 476 (98), 475 (30), 474 (100).

Example 24

Preparation of 8-(2-bromo-4-isopropylphenyl)-4-(ethylbutylamino)-2-methyl-5,6,7,8-tetrahydropteridine

A solution of the compound of Example 1 (650 mg, 1.41 mmol) in anhydrous tetrahydrofuran (5 mL) was treated with a tetrahydrofuran solution of borane (3 mL, 1 M, 3 mmol). The resulting solution was allowed to stir for 20 h, then was delivered slowly to stirring aq. 1 N sodium bicarbonate (10 mL). The mixture was stirred until gas evolution was complete, then was extracted with dichloromethane (twice 30 mL). The organic extracts were combined, dried over sodium sulfate, filtered and evaporated. The residual material was purified by elution through a short plug of silica gel (30:70 ethyl acetate-hexane), and evaporation gave the pure title product as an oil (429 mg, 1.04 mmol, 74%). Spectral data: TLC R_F 0.50 (30:70 ethyl acetate-hexane). ^1H NMR (300 MHz, $CDCl_3$): δ 7.50 (1H, d, J = 1.8 Hz), 7.24 (1H, d, J = 8.4 Hz), 7.18 (1H, dd, J = 8.4, 1.8 Hz), 3.88-3.39 (5H, br m), 3.22-3.09 (4H, m), 2.91 (1H, heptet, J = 7.0 Hz), 2.25 (3H, s), 1.52-1.41 (2H, m), 1.38-1.24 (2H, m), 1.27 (6H, d, J = 7.0 Hz), 1.08 (3H, t, J = 7.1 Hz), 0.91 (3H, t, J = 7.0 Hz). MS (ESI): *m/e* 450 (3), 449 (23), 448 (98), 447 (25), 446 (100). A solid derivative was obtained by precipitation of the hydrochloride salt from ether, melting point 79-81 °C.

Example 17

Preparation of 8-(2-bromo-4-isopropylphenyl)-2-methyl-4-(2-trifluoromethylphenyl)-5,6,7,8-tetrahydropteridin-6-one

Part A. A solution of 2-trifluoromethylphenylboronic acid (prepared according to the methods described in the review by N. Miyaura and A.

Suzuki, *Chem. Rev.* **1995**, *95*, p. 2457) (1.00 g, 5.27 mmol), 4,6-dichloro-2-methyl-5-nitropyrimidine (0.91 g, 4.39 mmol) and tetrakis(triphenyl-phosphine) palladium (147 mg) in benzene (15 mL) was treated with aq. sodium carbonate solution (6 mL, 1 M). This mixture was heated to reflux for 6 h, then cooled and partitioned between water and ethyl acetate (60 mL each). The organic layer was washed with brine, and the aqueous layers were back-extracted in sequence with more ethyl acetate. The organic extracts were combined, dried over sodium sulfate, filtered and evaporated. The residue was separated by column chromatography (silica gel, 15:85 ethyl acetate-hexane) to afford 4-chloro-2-methyl-5-nitro-6-(2-trifluoromethylphenyl)pyrimidine (0.64 g, 2.01 mmol, 38%) as a waxy solid. Spectral data: R_F 0.40 (20:80 ethyl acetate-hexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84-7.81 (1H, m), 7.69-7.63 (2H, m), 7.38-7.35 (1H, m), 2.84 (3H, s). MS (NH_3-CI) *m/e* 320 (24), 319 (26), 318 (100).

Part B. A solution of the compound prepared in Part A above (1.07 g, 3.37 mmol) and 2-bromo-4-isopropylaniline (0.87 g, 4.04 mmol) in tetrahydrofuran (20 mL) was heated to reflux for 5 h, then cooled and poured into 100 mL ethyl acetate. This was washed with aq. sodium bicarbonate solution (100 mL, 1 N) and brine, then dried over sodium sulfate, filtered and evaporated. The resulting solid was triturated with 1:1 petroleum ether-diethyl ether, filtered and dried under vacuum to afford pure 4-(2-bromo-4-isopropylphenylamino)-2-methyl-5-nitro-6-(2-trifluoromethylphenyl)pyrimidine (1.51 g, 3.05 mmol, 90%). Spectral data: m.p. 152-154 °C. R_F 0.37 (20:80 ethyl acetate-hexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.20 (1H, br s), 8.26 (1H, d, J = 8.4 Hz), 7.78 (1H, d, J = 7.7 Hz), 7.65-7.57 (2H, m), 7.52 (1H, d, J = 1.8 Hz), 7.35 (1H, d, J = 7.0 Hz), 7.28 (1H, br s), 2.93 (1H, m), 2.66 (3H, s), 1.29 (6H, d, J = 7.0 Hz). MS (NH_3-CI) *m/e* 498 (24), 497 (100), 496 (28), 495 (100).

Part C. The same procedure used for the reduction of a nitro group in Example 1, Part C was employed here. Thus, the compound of Part B above was converted to 5-amino-4-(2-bromo-4-isopropylphenylamino)-2-methyl-6-(2-trifluoromethylphenyl) pyrimidine in 32% yield. Spectral data: R_F 0.11 (20:80 ethyl acetate-hexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.58 (1H, d, J = 8.4 Hz), 7.83 (1H, d, J = 7.7 Hz), 7.67-7.58 (3H, m), 7.43 (1H, d, J = 1.8 Hz), 7.41 (1H, s), 7.25 (1H, dd, J = 8.4, 1.8 Hz), 2.89 (1H, m), 2.83 (2H, br s), 2.59 (3H, s), 1.26 (6H, d, J = 7.0 Hz). MS (NH_3-CI) *m/e* 468 (24), 467 (100), 466 (30), 465 (99).

Part D. The same procedure used for the cyclization reaction of Example 1, Part D was employed here. Thus, the compound of Part C above was converted to the title compound in 60% yield. Spectral data: m.p. 238-239 °C. R_F 0.20 (50:50 ethyl acetate-hexane). ^{1}H NMR (300 MHz, $CDCl_3$) d 7.85 (1H, d, J = 8.4 Hz), 7.73-7.59 (3H, m), 7.48-7.41 (1H, m), 7.33 (1H, s), 7.30 (1H, s), 7.00 (1H, br s), 4.46 (1H, d, J = 16.8 Hz), 4.42 (1H, d, J = 16.8 Hz), 2.97 (1H, m), 2.40 (3H, s), 1.31 (6H, d, J = 6.6 Hz). MS (NH_3-CI) *m/e* 508 (26), 507 (100), 506 (30), 505 (99).

Example 42

Preparation of Diethyl 2-[8-(2-bromo-4-isopropylphenyl)-2-methyl-6-oxo-5,6,7,8-tetrahydropteridin-4-yl]malonate

Sodium hydride suspension in mineral oil was washed with hexane and dried under vacuum, then taken up in tetrahydrofuran. This mixture is cooled to 0 °C, and treated with diethyl malonate (1.1 eq.). After the evolution of hydrogen gas is complete, the resulting solution is treated with 8-(2-bromo-4-isopropylphenyl)-4-chloro-2-methyl-5,6,7,8-tetrahydropteridin-6-one (see Example SF445, Part A, below; 1.0 eq.). The solution is heated to reflux until thin-layer chromatography shows the consumption of the starting material is nearly

complete. The mixture is allowed to cool, and poured into saturated aqueous ammonium chloride solution. This is extracted twice with ethyl acetate, and the extracts are washed with brine, combined, dried over sodium sulfate, filtered and evaporated. The residue is separated by column chromatography to afford the title product.

Example 131

Preparation of 8-(2-bromo-4-isopropylphenyl)-4-(ethylbutylamino)-2-methyl-5,6,7,8-tetrahydropteridin-6-thione

A solution of the compound of Example 1 (323 mg, 0.70 mmol) in toluene (10 mL) was treated with Lawesson's Reagent (170 mg, 0.42 mmol). The resulting mixture was heated to reflux for 6 h, then cooled and evaporated. The residue was separated by column chromatography (silica gel, 10:90 ethyl acetate-hexane) to afford the title product, which was purified by recrystallization from ethyl acetate-hexane (280 mg, 0.59 mmol, 84%). Spectral data: m.p. 148-149 °C (ether-hexane). TLC R_F 0.31 (20:80 ethyl acetate-hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.01 (1H, br s), 7.51 (1H, s), 7.22 (2H, s), 4.77 (1H, br d, J = 15.7 Hz), 4.56 (1H, br d, J = 15.7 Hz), 3.40-3.22 (4H, m), 2.92 (1H, heptet, J = 7.0 Hz), 2.29 (3H, s), 1.62-1.52 (2H, m), 1.40-1.30 (2H, m), 1.28 (6H, d, J = 7.0 Hz), 1.18 (3H, t, J = 7.0 Hz), 0.95 (3H, t, J = 7.3 Hz). MS (NH_3-CI): *m/e* 479 (26), 478 (100), 477 (30), 476 (95). Analysis calc'd for $C_{22}H_{30}BrN_5S$: C, 55.46; H, 6.36; N, 14.70; found: C, 55.54; H, 6.38; N, 14.37.

Example 248

Preparation of 8-(2-bromo-4-isopropyl-phenyl)-4-(ethylbutylamino)-2-methyl-5,6,7,8-tetrahydropteridin-6-imine

The method of Robba et al., *Tetrahedron Letters* **1992**, *33*, p. 2803-2804 may be used here. Thus, a solution of the compound of Example 131 in tetrahydrofuran (0.5 M) is warmed to 55 °C, and treated with 1.5 equivalents of mercuric chloride. Then, ammonia gas is bubbled in, and addition is continued until five minutes after the appearance of precipitating mercuric sulfide. The reaction mixture is allowed to stir for an additional hour, then is cooled, filtered through celite and evaporated. The residue is triturated with a small amount of water, filtered and dried to afford the title compound.

Modifications of the procedures presented below for Examples 501, 698 and 704 may be used to prepare many of the compounds listed in Table III.

Example 501

Preparation of 10-[2-bromo-4-(1-methylethyl)phenyl]-4-butyl-9,10-dihydro-2-methyl-4*H*,8*H*-pyrazino[3,2,1-*de*]pteridine-5,8(6*H*)-dione

Part A. Sodium hydride (mineral oil dispersion, 48 mg, 1.00 mmol) was washed with hexane, dried under vacuum, and taken up in dimethylformamide (5 mL). To this was added with stirring a solution of 5-amino-4-(2-bromo-4-isopropylphenylamino)-6-chloro-2-methylpyrimidine (311 mg, 0.87 mmol) in dimethylformamide (5 mL). After stirring for 30 min., the mixture was treated with ethyl bromoacetate (0.10 mL, 0.90 mmol) in one portion. The mixture was allowed to stir for 18 h, then poured into water (100 mL). This was extracted twice with ethyl acetate (100 mL each), and the organic extracts were washed in sequence with

two portions of water (100 mL each) and brine (100 mL), then combined, dried over sodium sulfate, filtered, and evaporated. The residual material was separated by column chromatography (silica gel, 20:80 ethyl acetate-hexane) to afford two fractions, the first being ethyl (8-(2-bromo-4-isopropylphenyl)-4-chloro-2-methyl-6-oxo-5,6,7,8-tetrahydropteridin-5-yl)acetate (89 mg, 0.18 mmol, 21%), the second being 8-(2-bromo-4-isopropylphenyl)-4-chloro-2-methyl-5,6,7,8-tetrahydropteridin-6-one (89 mg, 0.22 mmol, 26%). Spectral data for the first fraction: TLC R_F 0.25 (30:70 ethyl acetate-hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.53 (1H, d, J = 1.8 Hz), 7.26 (1H, dd, J = 8.4, 1.8 Hz), 7.22 (1H, d, J = 8.4 Hz), 4.88 (1H, d, J = 15 Hz), 4.84 (1H, d, J = 15 Hz), 4.47 (1H, d, J = 15.4 Hz), 4.27 (1H, d, J = 15.4 Hz), 4.25 (2H, q, J = 7.3 Hz), 2.95 (1H, heptet, J = 7.0 Hz), 2.38 (3H, s), 1.29 (3H, t, J = 7.3 Hz), 1.28 (6H, d, J = 7.0 Hz). MS (NH_3-CI): *m/e* 486 (6), 485 (26), 484 (23), 483 (100), 482 (18), 481 (76).

Part B. A solution of the first fraction from Part A above (89 mg, 0.18 mmol) in butylamine (1.0 mL, 10.1 mmol) was treated with glacial acetic acid (0.011 mL, 0.19 mmol), and the resulting solution was heated to reflux for 20 h. The mixture was cooled and evaporated, and the residue was separated by column chromatography (silica gel, 15:85 ethyl acetate-hexane) to afford the title compound as a solid (50 mg, 0.10 mmol, 57%). Spectral data: m.p. 207-208 °C. TLC R_F 0.29 (30:70 ethyl acetate-hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.54 (1H, d, J = 1.8 Hz), 7.27 (1H, dd, J = 8.4, 1.8 Hz), 7.23 (1H, d, J 8.4 Hz), 4.66 (1H, d, J = 18.6 Hz), 4.55 (2H, br d, J = 17 Hz), 4.32 (1H, d, J = 16.5 Hz), 4.12 (2H, t, J = 7.5 Hz), 2.95 (1H, heptet, J = 7.0 Hz), 2.33 (3H, s), 1.70-1.59 (2H, m), 1.45-1.35 (2H, m), 1.29 (6H, d, J = 7.0 Hz), 0.96 (3H, t, J = 7.1 Hz). MS (NH_3-CI): *m/e* 476 (4), 475 (25), 474 (100), 473 (27), 472 (99). Analysis

calc'd for $C_{22}H_{26}BrN_5O_2$: C, 55.94; H, 5.56; N, 14.83; found: C, 54.13; H, 5.34; N, 13.98.

Example 698

Preparation of Diethyl 4-[2-bromo-4-(1-methylethyl)phenyl]-5,6,9,10-tetrahydro-2-methyl-6-oxo-4*H*,8*H*-pyrido[3,2,1-*de*]pteridine-10,10-dicarboxylate

Sodium hydride dispersion is washed free of oil with hexane and dried under vacuum. Dimethylformamide is added, and the mixture is cooled to 0 °C. A solution of the compound of Example 42 (0.45 eq. based on the sodium hydride) in dimethylformamide is added, and the mixture is stirred for one hour. Then, a solution of 1,2-dibromoethane (1.0 eq. based on the substrate) in dimethylformamide is added dropwise slowly. The mixture is allowed to stir overnight, then is poured into water. The resulting mixture is extracted twice with ethyl acetate, and the extracts are twice more washed with water in sequence, then brine, then combined, dried over sodium sulfate, filtered and evaporated. The residue is separated by column chromatography to give the title product.

Example 704

Preparation of 4-[2-bromo-4-(1-methylethyl)phenyl]-5,6,9,10-tetrahydro-10,10-bis(methoxymethyl)-2-methyl-4*H*,8*H*-pyrido[3,2,1-*de*]pteridine

Part A. A solution of the compound of Example 698 in methylene chloride is cooled to 0 °C, and a solution of diisobutylaluminum hydride (7 eq.) in methylene chloride is slowly added by syringe. The mixture is allowed to stir and warm to ambient temperature until the substrate is consumed, then the reaction mixture is slowly delivered to stirring ice-cold 1 N HCl solution. The mixture is then neutralized to pH 7 with solid sodium bicarbonate, and extracted twice with methylene

chloride. The extracts are combined, dried over sodium sulfate, filtered and evaporated. The residue is separated by column chromatography to afford 4-[2-bromo-4-(1-methylethyl)phenyl]-5,6,9,10-tetrahydro-10,10-bis(hydroxymethyl)-2-methyl-4*H*,8*H*-pyrido[3,2,1-*de*]pteridine.

Part B. Sodium hydride dispersion is washed free of oil with hexane, and dried under vacuum. Dimethylformamide is added, the suspension is cooled to 0 °C, and a solution of the compound of Part A above in dimethylformamide is slowly added. After stirring for 1 h, the mixture is treated with 2 eq. methyl iodide. The mixture is allowed to stir for at least 6 h, then poured into water. This is extracted twice with ethyl acetate, and the extracts are washed in sequence twice with water and once with brine, then combined, dried over sodium sulfate, filtered and evaporated. Chromatography is then used to isolate the title product.

Modifications of the procedures presented below for Examples 719 and 759 may be used to prepare many of the compounds listed in Table IV.

Example 719

Preparation of 5-[2-bromo-4-(1-methylethyl)phenyl]-*N*-butyl-*N*-ethyl-4,5-dihydro-7-methyltetrazolo[1,5-f]pteridin-9-amine

A solution of the compound of Example 1 (358 mg, 0.78 mmol) in tetrahydrofuran (10 mL) was treated with trimethylsilylazide (0.21 mL, 1.58 mmol), diethyl azodicarboxylate (0.25 mL, 1.59 mmol) and triphenylphosphine (408 mg, 1.56 mmol). The resulting solution was stirred for 20 h, then evaporated. The residual material was separated by column chromatography (silica gel, 20:80 ethyl acetate-hexane) to afford the title product as a low-melting solid (147 mg, 0.30 mmol, 39%). Spectral data: TLC R_F 0.37 (30:70 ethyl acetate-

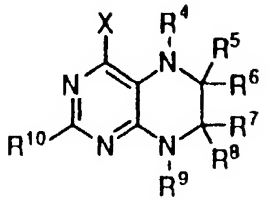
hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.52 (1H, d, J = 1.8 Hz), 7.26 (1H, dd, J = 8.0, 1.8 Hz), 7.21 (1H, d, J = 8.0 Hz), 5.23 (1H, d, J = 15.0 Hz), 4.98 (1H, d, J = 15.0 Hz), 3.56-3.48 (4H, m), 2.94 (1H, heptet, J = 7.0 Hz), 2.28 (3H, s), 1.69-1.59 (2H, m), 1.35-1.25 (2H, m), 1.29 (6H, d, J = 7.0 Hz), 1.21 (3H, t, J = 7.1 Hz), 0.90 (3H, t, J = 7.3 Hz). MS (NH_3-CI): *m/e* 488 (17), 487 (64), 486 (18), 485 (63), 459 (100), 457 (97).

Example 759

Preparation of 5-[2-bromo-4-(1-methylethyl)phenyl]-*N*-butyl-*N*-ethyl-5,6-dihydro-3-methylimidazo[1,2-*f*]pteridin-1-amine

A solution of the compound of Example 248 and a slight excess of bromoacetaldehyde diethyl acetal in ethanol is heated to reflux until the starting material is consumed. The reaction mixture is evaporated, and the residual material is purified by chromatography or recrystallization to afford the title product.

Table I.



Ex No	X	R^4	R^5	R^6	R^7	R^8	$R^{9\,a}$	R^{10}	mp, °C
1	$C_4H_9(C_2H_5)N$	H	=O	---	H	H	A	CH_3	146-147
2	$(CH_3)_2N$	H	=O	---	H	H	A	CH_3	---
3	$(C_2H_5)_2N$	H	=O	---	H	H	A	CH_3	---
4	$(C_4H_9)_2N$	H	=O	---	H	H	A	CH_3	---
5	$CH_3OCH_2CH(C_2H_5)NH$	H	=O	---	H	H	A	CH_3	197-198
6	$(CH_3O(CH_2)_2)_2N$	H	=O	---	H	H	A	CH_3	v. oil [b]
7	$(CH_3)_2NCH_2CH(C_3H_7)NH$	H	=O	---	H	H	A	CH_3	188-189
8	$C_6H_5CH_2(C_2H_5)NH$	H	=O	---	H	H	A	CH_3	---
9	$(c\text{-}C_3H_7)CH_2(C_2H_5)NH$	H	=O	---	H	H	A	CH_3	---
10	$(C_2H_5)_2CHNH$	H	=O	---	H	H	A	CH_3	---
11	C_4H_9	H	=O	---	H	H	A	CH_3	---
12	CH_3	H	=O	---	H	H	A	CH_3	---
13	$(C_2H_5)_2CH$	H	=O	---	H	H	A	CH_3	---
14	C_6H_5	H	=O	---	H	H	A	CH_3	---
15	$o\text{-}ClC_6H_4$	H	=O	---	H	H	A	CH_3	---
16	$o\text{-}NO_2\text{-}C_6H_4$	H	=O	---	H	H	A	CH_3	---
17	$o\text{-}CF_3\text{-}C_6H_4$	H	=O	---	H	H	A	CH_3	238-239

18	$2\text{-}C_5H_4N$	H	=O	---	H	H	A	CH_3	---
19	$(C_2H_5OC(=O))_2CH$	H	=O	---	H	H	A	CH_3	---
20	$(CN)_2CH$	H	=O	---	H	H	A	CH_3	---
21	$(CH_3OCH_2)_2CH$	H	=O	---	H	H	A	CH_3	---
22	CH_3S	H	=O	---	H	H	A	CH_3	---
23	$(C_2H_5)_2CHO$	H	=O	---	H	H	A	CH_3	---
24	$C_4H_9(C_2H_5)N$	H	H	H	H	H	A	CH_3	79-81 [c]
25	$(CH_3)_2N$	H	H	H	H	H	A	CH_3	---
26	$(C_2H_5)_2N$	H	H	H	H	H	A	CH_3	---
27	$(C_4H_9)_2N$	H	H	H	H	H	A	CH_3	---
28	$CH_3OCH_2CH(C_2H_5)NH$	H	H	H	H	H	A	CH_3	140-145
29	$(CH_3O(CH_2)_2)_2N$	H	H	H	H	H	A	CH_3	v. oil [d]
30	$(CH_3)_2NCH_2CH(C_3H_7)NH$	H	H	H	H	H	A	CH_3	83-85
31	$C_6H_5CH_2(C_2H_5)NH$	H	H	H	H	H	A	CH_3	---
32	$(c\text{-}C_3H_7)CH_2(C_2H_5)NH$	H	H	H	H	H	A	CH_3	---
33	$(C_2H_5)_2CHNH$	H	H	H	H	H	A	CH_3	---
34	C_4H_9NH	H	H	H	H	H	A	CH_3	160-162
35	CH_3	H	H	H	H	H	A	CH_3	---
36	$(C_2H_5)_2CH$	H	H	H	H	H	A	CH_3	---
37	C_6H_5	H	H	H	H	H	A	CH_3	---
38	$o\text{-}ClC_6H_4$	H	H	H	H	H	A	CH_3	---
39	$o\text{-}NO_2\text{-}C_6H_4$	H	H	H	H	H	A	CH_3	---
40	$o\text{-}CF_3\text{-}C_6H_4$	H	H	H	H	H	A	CH_3	108-110
41	$2\text{-}C_5H_4N$	H	H	H	H	H	A	CH_3	---
42	$(C_2H_5OC(=O))_2CH$	H	H	H	H	H	A	CH_3	---

43	$(CN)_2CH$	H	H	H	H	H	A	CH_3	---
44	$(CH_3OCH_2)_2CH$	H	H	H	H	H	A	CH_3	---
45	CH_3S	H	H	H	H	H	A	CH_3	---
46	$(C_2H_5)_2CHO$	H	H	H	H	H	A	CH_3	---
47	$C_4H_9(C_2H_5)N$	H	=O	---	H	H	B	CH_3	171-173
48	$CH_3OCH_2CH(C_2H_5)NH$	H	=O	---	H	H	B	CH_3	---
49	$(CH_3O(CH_2)_2)_2N$	H	=O	---	H	H	B	CH_3	---
50	$(CH_3)_2NCH_2CH(C_3H_7)NH$	H	=O	---	H	H	B	CH_3	---
51	o-CF_3-C_6H_4	H	=O	---	H	H	B	CH_3	---
52	$(C_2H_5)_2CHNH$	H	=O	---	H	H	B	CH_3	---
53	$C_4H_9(C_2H_5)N$	H	H	H	H	H	B	CH_3	99-100
54	$CH_3OCH_2CH(C_2H_5)NH$	H	H	H	H	H	B	CH_3	---
55	$(CH_3O(CH_2)_2)_2N$	H	H	H	H	H	B	CH_3	---
56	$(CH_3)_2NCH_2CH(C_3H_7)NH$	H	H	H	H	H	B	CH_3	---
57	o-CF_3-C_6H_4	H	H	H	H	H	B	CH_3	---
58	$(C_2H_5)_2CHNH$	H	H	H	H	H	B	CH_3	---
59	$C_4H_9(C_2H_5)N$	H	=O	---	H	H	C	CH_3	157-159
60	$CH_3OCH_2CH(C_2H_5)NH$	H	=O	---	H	H	C	CH_3	---
61	$(CH_3O(CH_2)_2)_2N$	H	=O	---	H	H	C	CH_3	v. oil [e]
62	$(CH_3)_2NCH_2CH(C_3H_7)NH$	H	=O	---	H	H	C	CH_3	---
63	o-CF_3-C_6H_4	H	=O	---	H	H	C	CH_3	---
64	$(C_2H_5)_2CHNH$	H	=O	---	H	H	C	CH_3	---
65	$C_4H_9(C_2H_5)N$	H	H	H	H	H	C	CH_3	v. oil [f]
66	$CH_3OCH_2CH(C_2H_5)NH$	H	H	H	H	H	C	CH_3	---
67	$(CH_3O(CH_2)_2)_2N$	H	H	H	H	H	C	CH_3	v. oil [g]

68	$(CH_3)_2NCH_2CH(C_3H_7)NH$	H	H	H	H	H	C	CH_3	---
69	o-CF_3-C_6H_4	H	H	H	H	H	C	CH_3	---
70	$(C_2H_5)_2CHNH$	H	H	H	H	H	C	CH_3	---
71	$C_4H_9(C_2H_5)N$	H	=O	---	H	H	D	CH_3	v. oil [h]
72	$CH_3OCH_2CH(C_2H_5)NH$	H	=O	---	H	H	D	CH_3	209-210
73	$(CH_3O(CH_2)_2)_2N$	H	=O	---	H	H	D	CH_3	---
74	$(CH_3)_2NCH_2CH(C_3H_7)NH$	H	=O	---	H	H	D	CH_3	---
75	o-CF_3-C_6H_4	H	=O	---	H	H	D	CH_3	---
76	$(C_2H_5)_2CHNH$	H	=O	---	H	H	D	CH_3	---
77	$C_4H_9(C_2H_5)N$	H	H	H	H	H	D	CH_3	---
78	$CH_3OCH_2CH(C_2H_5)NH$	H	H	H	H	H	D	CH_3	---
79	$(CH_3O(CH_2)_2)_2N$	H	H	H	H	H	D	CH_3	---
80	$(CH_3)_2NCH_2CH(C_3H_7)NH$	H	H	H	H	H	D	CH_3	---
81	o-CF_3-C_6H_4	H	H	H	H	H	D	CH_3	---
82	$(C_2H_5)_2CHNH$	H	H	H	H	H	D	CH_3	---
83	$C_4H_9(C_2H_5)N$	H	=O	---	H	H	E	CH_3	---
84	$CH_3OCH_2CH(C_2H_5)NH$	H	=O	---	H	H	E	CH_3	107-109
85	$(CH_3O(CH_2)_2)_2N$	H	=O	---	H	H	E	CH_3	---
86	$(CH_3)_2NCH_2CH(C_3H_7)NH$	H	=O	---	H	H	E	CH_3	---
87	o-CF_3-C_6H_4	H	=O	---	H	H	E	CH_3	---
88	$(C_2H_5)_2CHNH$	H	=O	---	H	H	E	CH_3	---
89	$C_4H_9(C_2H_5)N$	H	H	H	H	H	E	CH_3	---
90	$CH_3OCH_2CH(C_2H_5)NH$	H	H	H	H	H	E	CH_3	---
91	$(CH_3O(CH_2)_2)_2N$	H	H	H	H	H	E	CH_3	---
92	$(CH_3)_2NCH_2CH(C_3H_7)NH$	H	H	H	H	H	E	CH_3	---

93	o-CF_3-C_6H_4	H	H	H	H	H	E	CH_3	---
94	$(C_2H_5)_2CHNH$	H	H	H	H	H	E	CH_3	---
95	$C_4H_9(C_2H_5)N$	H	=O	---	H	H	F	CH_3	---
96	$CH_3OCH_2CH(C_2H_5)NH$	H	=O	---	H	H	F	CH_3	227-229
97	$(CH_3O(CH_2)_2)_2N$	H	=O	---	H	H	F	CH_3	---
98	$(CH_3)_2NCH_2CH(C_3H_7)NH$	H	=O	---	H	H	F	CH_3	---
99	o-CF_3-C_6H_4	H	=O	---	H	H	F	CH_3	---
100	$(C_2H_5)_2CHNH$	H	=O	---	H	H	F	CH_3	---
101	$C_4H_9(C_2H_5)N$	H	H	H	H	H	F	CH_3	---
102	$CH_3OCH_2CH(C_2H_5)NH$	H	H	H	H	H	F	CH_3	102-103
103	$(CH_3O(CH_2)_2)_2N$	H	H	H	H	H	F	CH_3	---
104	$(CH_3)_2NCH_2CH(C_3H_7)NH$	H	H	H	H	H	F	CH_3	---
105	o-CF_3-C_6H_4	H	H	H	H	H	F	CH_3	---
106	$(C_2H_5)_2CHNH$	H	H	H	H	H	F	CH_3	---
107	$C_4H_9(C_2H_5)N$	H	=O	---	H	H	G	CH_3	---
108	$CH_3OCH_2CH(C_2H_5)NH$	H	=O	---	H	H	G	CH_3	---
109	$(CH_3O(CH_2)_2)_2N$	H	=O	---	H	H	G	CH_3	---
110	$(CH_3)_2NCH_2CH(C_3H_7)NH$	H	=O	---	H	H	G	CH_3	---
111	o-CF_3-C_6H_4	H	=O	---	H	H	G	CH_3	---
112	$(C_2H_5)_2CHNH$	H	=O	---	H	H	G	CH_3	---
113	$C_4H_9(C_2H_5)N$	H	H	H	H	H	G	CH_3	---
114	$CH_3OCH_2CH(C_2H_5)NH$	H	H	H	H	H	G	CH_3	---
115	$(CH_3O(CH_2)_2)_2N$	H	H	H	H	H	G	CH_3	---
116	$(CH_3)_2NCH_2CH(C_3H_7)NH$	H	H	H	H	H	G	CH_3	---
117	o-CF_3-C_6H_4	H	H	H	H	H	G	CH_3	---

118	$(C_2H_5)_2CHNH$	H	H	H	H	H	G	CH_3	---
119	$C_4H_9(C_2H_5)N$	H	=O	---	H	H	J	CH_3	---
120	$CH_3OCH_2CH(C_2H_5)NH$	H	=O	---	H	H	J	CH_3	---
121	$(CH_3O(CH_2)_2)_2N$	H	=O	---	H	H	J	CH_3	---
122	$(CH_3)_2NCH_2CH(C_3H_7)NH$	H	=O	---	H	H	J	CH_3	---
123	o-CF_3-C_6H_4	H	=O	---	H	H	J	CH_3	---
124	$(C_2H_5)_2CHNH$	H	=O	---	H	H	J	CH_3	---
125	$C_4H_9(C_2H_5)N$	H	H	H	H	H	J	CH_3	---
126	$CH_3OCH_2CH(C_2H_5)NH$	H	H	H	H	H	J	CH_3	---
127	$(CH_3O(CH_2)_2)_2N$	H	H	H	H	H	J	CH_3	---
128	$(CH_3)_2NCH_2CH(C_3H_7)NH$	H	H	H	H	H	J	CH_3	---
129	o-CF_3-C_6H_4	H	H	H	H	H	J	CH_3	---
130	$(C_2H_5)_2CHNH$	H	H	H	H	H	J	CH_3	---
131	$C_4H_9(C_2H_5)N$	H	=S	---	H	H	A	CH_3	148-149
132	$CH_3OCH_2CH(C_2H_5)NH$	H	=S	---	H	H	A	CH_3	---
133	$(CH_3O(CH_2)_2)_2N$	H	=S	---	H	H	A	CH_3	---
134	$(CH_3)_2NCH_2CH(C_3H_7)NH$	H	=S	---	H	H	A	CH_3	---
135	o-CF_3-C_6H_4	H	=S	---	H	H	A	CH_3	---
136	$(C_2H_5)_2CHNH$	H	=S	---	H	H	A	CH_3	---
137	$C_4H_9(C_2H_5)N$	CH_3	=S	---	H	H	A	CH_3	v. oil
138	$CH_3OCH_2CH(C_2H_5)NH$	CH_3	=S	---	H	H	A	CH_3	---
139	$(CH_3O(CH_2)_2)_2N$	CH_3	=S	---	H	H	A	CH_3	---
140	$(CH_3)_2NCH_2CH(C_3H_7)NH$	CH_3	=S	---	H	H	A	CH_3	---
141	o-CF_3-C_6H_4	CH_3	=S	---	H	H	A	CH_3	---
142	$(C_2H_5)_2CHNH$	CH_3	=S	---	H	H	A	CH_3	---

143	$C_4H_9(C_2H_5)N$	CH_3	=O	---	H	H	A	CH_3	v. oil [j]
144	$CH_3OCH_2CH(C_2H_5)NH$	CH_3	=O	---	H	H	A	CH_3	---
145	$(CH_3O(CH_2)_2)_2N$	CH_3	=O	---	H	H	A	CH_3	---
146	$(CH_3)_2NCH_2CH(C_3H_7)NH$	CH_3	=O	---	H	H	A	CH_3	---
147	o-CF_3-C_6H_4	CH_3	=O	---	H	H	A	CH_3	v. oil [k]
148	$(C_2H_5)_2CHNH$	CH_3	=O	---	H	H	A	CH_3	---
149	$C_4H_9(C_2H_5)N$	CH_3	H	H	H	H	A	CH_3	v. oil [l]
150	$CH_3OCH_2CH(C_2H_5)NH$	CH_3	H	H	H	H	A	CH_3	---
151	$(CH_3O(CH_2)_2)_2N$	CH_3	H	H	H	H	A	CH_3	---
152	$(CH_3)_2NCH_2CH(C_3H_7)NH$	CH_3	H	H	H	H	A	CH_3	---
153	o-CF_3-C_6H_4	CH_3	H	H	H	H	A	CH_3	108-110
154	$(C_2H_5)_2CHNH$	CH_3	H	H	H	H	A	CH_3	---
155	$C_4H_9(C_2H_5)N$	CH_3	=O	---	CH_3	H	A	CH_3	v. oil [m]
156	$CH_3OCH_2CH(C_2H_5)NH$	CH_3	=O	---	CH_3	H	A	CH_3	---
157	$(CH_3O(CH_2)_2)_2N$	CH_3	=O	---	CH_3	H	A	CH_3	---
158	$(CH_3)_2NCH_2CH(C_3H_7)NH$	CH_3	=O	---	CH_3	H	A	CH_3	---
159	o-CF_3-C_6H_4	CH_3	=O	---	CH_3	H	A	CH_3	v. oil [n]
160	$(C_2H_5)_2CHNH$	CH_3	=O	---	CH_3	H	A	CH_3	---
161	$C_4H_9(C_2H_5)N$	CH_3	H	H	CH_3	H	A	CH_3	---
162	$CH_3OCH_2CH(C_2H_5)NH$	CH_3	H	H	CH_3	H	A	CH_3	---
163	$(CH_3O(CH_2)_2)_2N$	CH_3	H	H	CH_3	H	A	CH_3	---
164	$(CH_3)_2NCH_2CH(C_3H_7)NH$	CH_3	H	H	CH_3	H	A	CH_3	---
165	o-CF_3-C_6H_4	CH_3	H	H	CH_3	H	A	CH_3	---
166	$(C_2H_5)_2CHNH$	CH_3	H	H	CH_3	H	A	CH_3	---
167	$C_4H_9(C_2H_5)N$	$CH_2CH=CH_2$	=O	---	H	H	A	CH_3	---

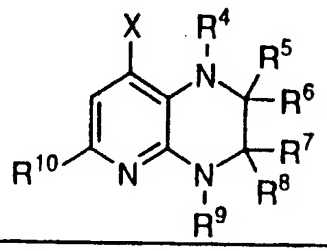
168	$CH_3OCH_2CH(C_2H_5)NH$	$CH_2CH=CH_2$	=O	---	H	H	A	CH_3	---
169	$(CH_3O(CH_2)_2)_2N$	$CH_2CH=CH_2$	=O	---	H	H	A	CH_3	---
170	$(CH_3)_2NCH_2CH(C_3H_7)NH$	$CH_2CH=CH_2$	=O	---	H	H	A	CH_3	---
171	o-CF_3-C_6H_4	$CH_2CH=CH_2$	=O	---	H	H	A	CH_3	167-168
172	$(C_2H_5)_2CHNH$	$CH_2CH=CH_2$	=O	---	H	H	A	CH_3	---
173	$C_4H_9(C_2H_5)N$	$CH_2CH=CH_2$	H	H	H	H	A	CH_3	---
174	$CH_3OCH_2CH(C_2H_5)NH$	$CH_2CH=CH_2$	H	H	H	H	A	CH_3	---
175	$(CH_3O(CH_2)_2)_2N$	$CH_2CH=CH_2$	H	H	H	H	A	CH_3	---
176	$(CH_3)_2NCH_2CH(C_3H_7)NH$	$CH_2CH=CH_2$	H	H	H	H	A	CH_3	---
177	o-CF_3-C_6H_4	$CH_2CH=CH_2$	H	H	H	H	A	CH_3	---
178	$(C_2H_5)_2CHNH$	$CH_2CH=CH_2$	H	H	H	H	A	CH_3	---
179	$C_4H_9(C_2H_5)N$	$CH_2CH=CH_2$	=O	---	$CH_2CH=CH_2$	H	A	CH_3	---
180	$CH_3OCH_2CH(C_2H_5)NH$	$CH_2CH=CH_2$	=O	---	$CH_2CH=CH_2$	H	A	CH_3	---
181	$(CH_3O(CH_2)_2)_2N$	$CH_2CH=CH_2$	=O	---	$CH_2CH=CH_2$	H	A	CH_3	---
182	$(CH_3)_2NCH_2CH(C_3H_7)NH$	$CH_2CH=CH_2$	=O	---	$CH_2CH=CH_2$	H	A	CH_3	---
183	o-CF_3-C_6H_4	CH_3	=O	---	$CH_2CH=CH_2$	H	A	CH_3	---
184	$(C_2H_5)_2CHNH$	$CH_2CH=CH_2$	=O	---	$CH_2CH=CH_2$	H	A	CH_3	---
185	$C_4H_9(C_2H_5)N$	$CH_2CH=CH_2$	H	H	$CH_2CH=CH_2$	H	A	CH_3	---
186	$CH_3OCH_2CH(C_2H_5)NH$	$CH_2CH=CH_2$	H	H	$CH_2CH=CH_2$	H	A	CH_3	---
187	$(CH_3O(CH_2)_2)_2N$	$CH_2CH=CH_2$	H	H	$CH_2CH=CH_2$	H	A	CH_3	---
188	$(CH_3)_2NCH_2CH(C_3H_7)NH$	$CH_2CH=CH_2$	H	H	$CH_2CH=CH_2$	H	A	CH_3	---
189	o-CF_3-C_6H_4	$CH_2CH=CH_2$	H	H	$CH_2CH=CH_2$	H	A	CH_3	---
190	$(C_2H_5)_2CHNH$	$CH_2CH=CH_2$	H	H	$CH_2CH=CH_2$	H	A	CH_3	---
191	$C_4H_9(C_2H_5)N$	H	CH_3	CH_3	H	H	A	CH_3	---
192	$CH_3OCH_2CH(C_2H_5)NH$	H	CH_3	CH_3	H	H	A	CH_3	---

193	$(CH_3O(CH_2)_2)_2N$	H	CH_3	CH_3	H	H	A	CH_3	---
194	$(CH_3)_2NCH_2CH(C_3H_7)NH$	H	CH_3	CH_3	H	H	A	CH_3	---
195	o-CF_3-C_6H_4	H	CH_3	CH_3	H	H	A	CH_3	---
196	$(C_2H_5)_2CHNH$	H	CH_3	CH_3	H	H	A	CH_3	---
197	$C_4H_9(C_2H_5)N$	H	=O	---	CH_3	CH_3	A	CH_3	---
198	$CH_3OCH_2CH(C_2H_5)NH$	H	=O	---	CH_3	CH_3	A	CH_3	---
199	$(CH_3O(CH_2)_2)_2N$	H	=O	---	CH_3	CH_3	A	CH_3	---
200	$(CH_3)_2NCH_2CH(C_3H_7)NH$	H	=O	---	CH_3	CH_3	A	CH_3	---
201	o-CF_3-C_6H_4	H	=O	---	CH_3	CH_3	A	CH_3	---
202	$(C_2H_5)_2CHNH$	H	=O	---	CH_3	CH_3	A	CH_3	---
203	$C_4H_9(C_2H_5)N$	H	H	H	CH_3	CH_3	A	CH_3	---
204	$CH_3OCH_2CH(C_2H_5)NH$	H	H	H	CH_3	CH_3	A	CH_3	---
205	$(CH_3O(CH_2)_2)_2N$	H	H	H	CH_3	CH_3	A	CH_3	---
206	$(CH_3)_2NCH_2CH(C_3H_7)NH$	H	H	H	CH_3	CH_3	A	CH_3	---
207	o-CF_3-C_6H_4	H	H	H	CH_3	CH_3	A	CH_3	---
208	$(C_2H_5)_2CHNH$	H	H	H	CH_3	CH_3	A	CH_3	---
209	$C_4H_9(C_2H_5)N$	H	=O	---	H	H	A	H	---
210	$CH_3OCH_2CH(C_2H_5)NH$	H	=O	---	H	H	A	H	---
211	$(CH_3O(CH_2)_2)_2N$	H	=O	---	H	H	A	H	---
212	$(CH_3)_2NCH_2CH(C_3H_7)NH$	H	=O	---	H	H	A	H	---
213	o-CF_3-C_6H_4	H	=O	---	H	H	A	H	---
214	$(C_2H_5)_2CHNH$	H	=O	---	H	H	A	H	---
215	$C_4H_9(C_2H_5)N$	H	H	H	H	H	A	H	---
216	$CH_3OCH_2CH(C_2H_5)NH$	H	H	H	H	H	A	H	---
217	$(CH_3O(CH_2)_2)_2N$	H	H	H	H	H	A	H	---

218	$(CH_3)_2NCH_2CH(C_3H_7)NH$	H	H	H	H	H	A	H	---
219	o-CF_3-C_6H_4	H	H	H	H	H	A	H	---
220	$(C_2H_5)_2CHNH$	H	H	H	H	H	A	H	---
221	$C_4H_9(C_2H_5)N$	H	=O	---	H	H	A	CN	---
222	$CH_3OCH_2CH(C_2H_5)NH$	H	=O	---	H	H	A	CN	---
223	$(CH_3O(CH_2)_2)_2N$	H	=O	---	H	H	A	CN	---
224	$(CH_3)_2NCH_2CH(C_3H_7)NH$	H	=O	---	H	H	A	CN	---
225	o-CF_3-C_6H_4	H	=O	---	H	H	A	CN	---
226	$(C_2H_5)_2CHNH$	H	=O	---	H	H	A	CN	---
227	$C_4H_9(C_2H_5)N$	H	H	H	H	H	A	CN	---
228	$CH_3OCH_2CH(C_2H_5)NH$	H	H	H	H	H	A	CN	---
229	$(CH_3O(CH_2)_2)_2N$	H	H	H	H	H	A	CN	---
230	$(CH_3)_2NCH_2CH(C_3H_7)NH$	H	H	H	H	H	A	CN	---
231	o-CF_3-C_6H_4	H	H	H	H	H	A	CN	---
232	$(C_2H_5)_2CHNH$	H	H	H	H	H	A	CN	---
233	2-morpholinyl	H	H	H	H	H	A	CH_3	60-62
234	2-morpholinyl	H	=O	---	H	H	B	CH_3	---
235	2-morpholinyl	H	=O	---	H	H	C	CH_3	---
236	2-morpholinyl	H	=O	---	H	H	D	CH_3	---
237	2-morpholinyl	H	=O	---	H	H	E	CH_3	---
238	2-morpholinyl	H	=O	---	H	H	F	CH_3	---
239	2-morpholinyl	H	=O	---	H	H	G	CH_3	---
240	2-morpholinyl	H	=O	---	H	H	J	CH_3	---
241	2-morpholinyl	H	H	H	H	H	B	CH_3	---
242	2-morpholinyl	H	H	H	H	H	C	CH_3	---

243	2-morpholinyl	H	H	H	H	H	D	CH_3	---
244	2-morpholinyl	H	H	H	H	H	E	CH_3	---
245	2-morpholinyl	H	H	H	H	H	F	CH_3	---
246	2-morpholinyl	H	H	H	H	H	G	CH_3	---
247	2-morpholinyl	H	H	H	H	H	J	CH_3	---
248	$C_4H_9(C_2H_5)N$	H	=NH	---	H	H	A	CH_3	---
249	$C_4H_9(C_2H_5)N$	H	=NH	---	H	H	C	CH_3	---
250	$C_4H_9(C_2H_5)N$	H	$=NC_4H_9$	---	H	H	A	CH_3	---

Table II.



Ex No	X	R^4	R^5	R^6	R^7	R^8	$R^{9\,a}$	R^{10}	mp, °C
251	$C_4H_9(C_2H_5)N$	H	=O	---	H	H	A	CH_3	---
252	$(CH_3)_2N$	H	=O	---	H	H	A	CH_3	---
253	$(C_2H_5)_2N$	H	=O	---	H	H	A	CH_3	---
254	$(C_4H_9)_2N$	H	=O	---	H	H	A	CH_3	---
255	$CH_3OCH_2CH(C_2H_5)NH$	H	=O	---	H	H	A	CH_3	---
256	$(CH_3O(CH_2)_2)_2N$	H	=O	---	H	H	A	CH_3	---
257	$(CH_3)_2NCH_2CH(C_3H_7)NH$	H	=O	---	H	H	A	CH_3	---
258	$C_6H_5CH_2(C_2H_5)NH$	H	=O	---	H	H	A	CH_3	---
259	$(c\text{-}C_3H_7)CH_2(C_2H_5)NH$	H	=O	---	H	H	A	CH_3	---
260	$(C_2H_5)_2CHNH$	H	=O	---	H	H	A	CH_3	---
261	C_4H_9	H	=O	---	H	H	A	CH_3	---
262	CH_3	H	=O	---	H	H	A	CH_3	---
263	$(C_2H_5)_2CH$	H	=O	---	H	H	A	CH_3	---
264	C_6H_5	H	=O	---	H	H	A	CH_3	---
265	$o\text{-}ClC_6H_4$	H	=O	---	H	H	A	CH_3	---
266	$o\text{-}NO_2\text{-}C_6H_4$	H	=O	---	H	H	A	CH_3	---
267	$o\text{-}CF_3\text{-}C_6H_4$	H	=O	---	H	H	A	CH_3	---

268	$2-C_5H_4N$	H	=O	---	H	H	A	CH_3	---
269	$(C_2H_5OC(=O))_2CH$	H	=O	---	H	H	A	CH_3	---
270	$(CN)_2CH$	H	=O	---	H	H	A	CH_3	---
271	$(CH_3OCH_2)_2CH$	H	=O	---	H	H	A	CH_3	---
272	CH_3S	H	=O	---	H	H	A	CH_3	---
273	$(C_2H_5)_2CHO$	H	=O	---	H	H	A	CH_3	---
274	$C_4H_9(C_2H_5)N$	H	H	H	H	H	A	CH_3	---
275	$(CH_3)_2N$	H	H	H	H	H	A	CH_3	---
276	$(C_2H_5)_2N$	H	H	H	H	H	A	CH_3	---
277	$(C_4H_9)_2N$	H	H	H	H	H	A	CH_3	---
278	$CH_3OCH_2CH(C_2H_5)NH$	H	H	H	H	H	A	CH_3	---
279	$(CH_3O(CH_2)_2)_2N$	H	H	H	H	H	A	CH_3	---
280	$(CH_3)_2NCH_2CH(C_3H_7)NH$	H	H	H	H	H	A	CH_3	---
281	$C_6H_5CH_2(C_2H_5)NH$	H	H	H	H	H	A	CH_3	---
282	$(c\text{-}C_3H_7)CH_2(C_2H_5)NH$	H	H	H	H	H	A	CH_3	---
283	$(C_2H_5)_2CHNH$	H	H	H	H	H	A	CH_3	---
284	C_4H_9NH	H	H	H	H	H	A	CH_3	---
285	CH_3	H	H	H	H	H	A	CH_3	---
286	$(C_2H_5)_2CH$	H	H	H	H	H	A	CH_3	---
287	C_6H_5	H	H	H	H	H	A	CH_3	---
288	$o\text{-}ClC_6H_4$	H	H	H	H	H	A	CH_3	---
289	$o\text{-}NO_2\text{-}C_6H_4$	H	H	H	H	H	A	CH_3	---
290	$o\text{-}CF_3\text{-}C_6H_4$	H	H	H	H	H	A	CH_3	---
291	$2-C_5H_4N$	H	H	H	H	H	A	CH_3	---
292	$(C_2H_5OC(=O))_2CH$	H	H	H	H	H	A	CH_3	---

293	$(CN)_2CH$	H	H	H	H	H	A	CH_3	---
294	$(CH_3OCH_2)_2CH$	H	H	H	H	H	A	CH_3	---
295	CH_3S	H	H	H	H	H	A	CH_3	---
296	$(C_2H_5)_2CHO$	H	H	H	H	H	A	CH_3	---
297	$C_4H_9(C_2H_5)N$	H	=O	---	H	H	B	CH_3	---
298	$CH_3OCH_2CH(C_2H_5)NH$	H	=O	---	H	H	B	CH_3	---
299	$(CH_3O(CH_2)_2)_2N$	H	=O	---	H	H	B	CH_3	---
300	$(CH_3)_2NCH_2CH(C_3H_7)NH$	H	=O	---	H	H	B	CH_3	---
301	o-CF_3-C_6H_4	H	=O	---	H	H	B	CH_3	---
302	$(C_2H_5)_2CHNH$	H	=O	---	H	H	B	CH_3	---
303	$C_4H_9(C_2H_5)N$	H	H	H	H	H	B	CH_3	---
304	$CH_3OCH_2CH(C_2H_5)NH$	H	H	H	H	H	B	CH_3	---
305	$(CH_3O(CH_2)_2)_2N$	H	H	H	H	H	B	CH_3	---
306	$(CH_3)_2NCH_2CH(C_3H_7)NH$	H	H	H	H	H	B	CH_3	---
307	o-CF_3-C_6H_4	H	H	H	H	H	B	CH_3	---
308	$(C_2H_5)_2CHNH$	H	H	H	H	H	B	CH_3	---
309	$C_4H_9(C_2H_5)N$	H	=O	---	H	H	C	CH_3	---
310	$CH_3OCH_2CH(C_2H_5)NH$	H	=O	---	H	H	C	CH_3	---
311	$(CH_3O(CH_2)_2)_2N$	H	=O	---	H	H	C	CH_3	---
312	$(CH_3)_2NCH_2CH(C_3H_7)NH$	H	=O	---	H	H	C	CH_3	---
313	o-CF_3-C_6H_4	H	=O	---	H	H	C	CH_3	---
314	$(C_2H_5)_2CHNH$	H	=O	---	H	H	C	CH_3	---
315	$C_4H_9(C_2H_5)N$	H	H	H	H	H	C	CH_3	---
316	$CH_3OCH_2CH(C_2H_5)NH$	H	H	H	H	H	C	CH_3	---
317	$(CH_3O(CH_2)_2)_2N$	H	H	H	H	H	C	CH_3	---

318	$(CH_3)_2NCH_2CH(C_3H_7)NH$	H	H	H	H	H	C	CH_3	---
319	o-CF_3-C_6H_4	H	H	H	H	H	C	CH_3	---
320	$(C_2H_5)_2CHNH$	H	H	H	H	H	C	CH_3	---
321	$C_4H_9(C_2H_5)N$	H	=O	---	H	H	D	CH_3	---
322	$CH_3OCH_2CH(C_2H_5)NH$	H	=O	---	H	H	D	CH_3	---
323	$(CH_3O(CH_2)_2)_2N$	H	=O	---	H	H	D	CH_3	---
324	$(CH_3)_2NCH_2CH(C_3H_7)NH$	H	=O	---	H	H	D	CH_3	---
325	o-CF_3-C_6H_4	H	=O	---	H	H	D	CH_3	---
326	$(C_2H_5)_2CHNH$	H	=O	---	H	H	D	CH_3	---
327	$C_4H_9(C_2H_5)N$	H	H	H	H	H	D	CH_3	---
328	$CH_3OCH_2CH(C_2H_5)NH$	H	H	H	H	H	D	CH_3	---
329	$(CH_3O(CH_2)_2)_2N$	H	H	H	H	H	D	CH_3	---
330	$(CH_3)_2NCH_2CH(C_3H_7)NH$	H	H	H	H	H	D	CH_3	---
331	o-CF_3-C_6H_4	H	H	H	H	H	D	CH_3	---
332	$(C_2H_5)_2CHNH$	H	H	H	H	H	D	CH_3	---
333	$C_4H_9(C_2H_5)N$	H	=O	---	H	H	E	CH_3	---
334	$CH_3OCH_2CH(C_2H_5)NH$	H	=O	---	H	H	E	CH_3	---
335	$(CH_3O(CH_2)_2)_2N$	H	=O	---	H	H	E	CH_3	---
336	$(CH_3)_2NCH_2CH(C_3H_7)NH$	H	=O	---	H	H	E	CH_3	---
337	o-CF_3-C_6H_4	H	=O	---	H	H	E	CH_3	---
338	$(C_2H_5)_2CHNH$	H	=O	---	H	H	E	CH_3	---
339	$C_4H_9(C_2H_5)N$	H	H	H	H	H	E	CH_3	---
340	$CH_3OCH_2CH(C_2H_5)NH$	H	H	H	H	H	E	CH_3	---
341	$(CH_3O(CH_2)_2)_2N$	H	H	H	H	H	E	CH_3	---
342	$(CH_3)_2NCH_2CH(C_3H_7)NH$	H	H	H	H	H	E	CH_3	---

343	o-CF_3-C_6H_4	H	H	H	H	H	E	CH_3	---
344	$(C_2H_5)_2CHNH$	H	H	H	H	H	E	CH_3	---
345	$C_4H_9(C_2H_5)N$	H	=O	---	H	H	F	CH_3	---
346	$CH_3OCH_2CH(C_2H_5)NH$	H	=O	---	H	H	F	CH_3	---
347	$(CH_3O(CH_2)_2)_2N$	H	=O	---	H	H	F	CH_3	---
348	$(CH_3)_2NCH_2CH(C_3H_7)NH$	H	=O	---	H	H	F	CH_3	---
349	o-CF_3-C_6H_4	H	=O	---	H	H	F	CH_3	---
350	$(C_2H_5)_2CHNH$	H	=O	---	H	H	F	CH_3	---
351	$C_4H_9(C_2H_5)N$	H	H	H	H	H	F	CH_3	---
352	$CH_3OCH_2CH(C_2H_5)NH$	H	H	H	H	H	F	CH_3	---
353	$(CH_3O(CH_2)_2)_2N$	H	H	H	H	H	F	CH_3	---
354	$(CH_3)_2NCH_2CH(C_3H_7)NH$	H	H	H	H	H	F	CH_3	---
355	o-CF_3-C_6H_4	H	H	H	H	H	F	CH_3	---
356	$(C_2H_5)_2CHNH$	H	H	H	H	H	F	CH_3	---
357	$C_4H_9(C_2H_5)N$	H	=O	---	H	H	G	CH_3	---
358	$CH_3OCH_2CH(C_2H_5)NH$	H	=O	---	H	H	G	CH_3	---
359	$(CH_3O(CH_2)_2)_2N$	H	=O	---	H	H	G	CH_3	---
360	$(CH_3)_2NCH_2CH(C_3H_7)NH$	H	=O	---	H	H	G	CH_3	---
361	o-CF_3-C_6H_4	H	=O	---	H	H	G	CH_3	---
362	$(C_2H_5)_2CHNH$	H	=O	---	H	H	G	CH_3	---
363	$C_4H_9(C_2H_5)N$	H	H	H	H	H	G	CH_3	---
364	$CH_3OCH_2CH(C_2H_5)NH$	H	H	H	H	H	G	CH_3	---
365	$(CH_3O(CH_2)_2)_2N$	H	H	H	H	H	G	CH_3	---
366	$(CH_3)_2NCH_2CH(C_3H_7)NH$	H	H	H	H	H	G	CH_3	---
367	o-CF_3-C_6H_4	H	H	H	H	H	G	CH_3	---

368	$(C_2H_5)_2CHNH$	H	H	H	H	H	G	CH_3	---
369	$C_4H_9(C_2H_5)N$	H	=O	---	H	H	J	CH_3	---
370	$CH_3OCH_2CH(C_2H_5)NH$	H	=O	---	H	H	J	CH_3	---
371	$(CH_3O(CH_2)_2)_2N$	H	=O	---	H	H	J	CH_3	---
372	$(CH_3)_2NCH_2CH(C_3H_7)NH$	H	=O	---	H	H	J	CH_3	---
373	o-CF_3-C_6H_4	H	=O	---	H	H	J	CH_3	---
374	$(C_2H_5)_2CHNH$	H	=O	---	H	H	J	CH_3	---
375	$C_4H_9(C_2H_5)N$	H	H	H	H	H	J	CH_3	---
376	$CH_3OCH_2CH(C_2H_5)NH$	H	H	H	H	H	J	CH_3	---
377	$(CH_3O(CH_2)_2)_2N$	H	H	H	H	H	J	CH_3	---
378	$(CH_3)_2NCH_2CH(C_3H_7)NH$	H	H	H	H	H	J	CH_3	---
379	o-CF_3-C_6H_4	H	H	H	H	H	J	CH_3	---
380	$(C_2H_5)_2CHNH$	H	H	H	H	H	J	CH_3	---
381	$C_4H_9(C_2H_5)N$	H	=S	---	H	H	A	CH_3	---
382	$CH_3OCH_2CH(C_2H_5)NH$	H	=S	---	H	H	A	CH_3	---
383	$(CH_3O(CH_2)_2)_2N$	H	=S	---	H	H	A	CH_3	---
384	$(CH_3)_2NCH_2CH(C_3H_7)NH$	H	=S	---	H	H	A	CH_3	---
385	o-CF_3-C_6H_4	H	=S	---	H	H	A	CH_3	---
386	$(C_2H_5)_2CHNH$	H	=S	---	H	H	A	CH_3	---
387	$C_4H_9(C_2H_5)N$	CH_3	=S	---	H	H	A	CH_3	---
388	$CH_3OCH_2CH(C_2H_5)NH$	CH_3	=S	---	H	H	A	CH_3	---
389	$(CH_3O(CH_2)_2)_2N$	CH_3	=S	---	H	H	A	CH_3	---
390	$(CH_3)_2NCH_2CH(C_3H_7)NH$	CH_3	=S	---	H	H	A	CH_3	---
391	o-CF_3-C_6H_4	CH_3	=S	---	H	H	A	CH_3	---
392	$(C_2H_5)_2CHNH$	CH_3	=S	---	H	H	A	CH_3	---

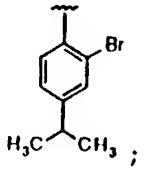
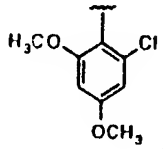
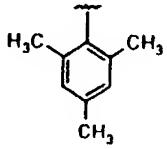
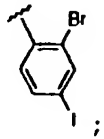
393	$C_4H_9(C_2H_5)N$	CH_3	=O	---	H	H	A	CH_3	---
394	$CH_3OCH_2CH(C_2H_5)NH$	CH_3	=O	---	H	H	A	CH_3	---
395	$(CH_3O(CH_2)_2)_2N$	CH_3	=O	---	H	H	A	CH_3	---
396	$(CH_3)_2NCH_2CH(C_3H_7)NH$	CH_3	=O	---	H	H	A	CH_3	---
397	o-CF_3-C_6H_4	CH_3	=O	---	H	H	A	CH_3	---
398	$(C_2H_5)_2CHNH$	CH_3	=O	---	H	H	A	CH_3	---
399	$C_4H_9(C_2H_5)N$	CH_3	H	H	H	H	A	CH_3	---
400	$CH_3OCH_2CH(C_2H_5)NH$	CH_3	H	H	H	H	A	CH_3	---
401	$(CH_3O(CH_2)_2)_2N$	CH_3	H	H	H	H	A	CH_3	---
402	$(CH_3)_2NCH_2CH(C_3H_7)NH$	CH_3	H	H	H	H	A	CH_3	---
403	o-CF_3-C_6H_4	CH_3	H	H	H	H	A	CH_3	---
404	$(C_2H_5)_2CHNH$	CH_3	H	H	H	H	A	CH_3	---
405	$C_4H_9(C_2H_5)N$	CH_3	=O	---	CH_3	H	A	CH_3	---
406	$CH_3OCH_2CH(C_2H_5)NH$	CH_3	=O	---	CH_3	H	A	CH_3	---
407	$(CH_3O(CH_2)_2)_2N$	CH_3	=O	---	CH_3	H	A	CH_3	---
408	$(CH_3)_2NCH_2CH(C_3H_7)NH$	CH_3	=O	---	CH_3	H	A	CH_3	---
409	o-CF_3-C_6H_4	CH_3	=O	---	CH_3	H	A	CH_3	---
410	$(C_2H_5)_2CHNH$	CH_3	=O	---	CH_3	H	A	CH_3	---
411	$C_4H_9(C_2H_5)N$	CH_3	H	H	CH_3	H	A	CH_3	---
412	$CH_3OCH_2CH(C_2H_5)NH$	CH_3	H	H	CH_3	H	A	CH_3	---
413	$(CH_3O(CH_2)_2)_2N$	CH_3	H	H	CH_3	H	A	CH_3	---
414	$(CH_3)_2NCH_2CH(C_3H_7)NH$	CH_3	H	H	CH_3	H	A	CH_3	---
415	o-CF_3-C_6H_4	CH_3	H	H	CH_3	H	A	CH_3	---
416	$(C_2H_5)_2CHNH$	CH_3	H	H	CH_3	H	A	CH_3	---
417	$C_4H_9(C_2H_5)N$	$CH_2CH=CH_2$	=O	---	H	H	A	CH_3	---

418	$CH_3OCH_2CH(C_2H_5)NH$	$CH_2CH=CH_2$	=O	---	H	H	A	CH_3	---
419	$(CH_3O(CH_2)_2)_2N$	$CH_2CH=CH_2$	=O	---	H	H	A	CH_3	---
420	$(CH_3)_2NCH_2CH(C_3H_7)NH$	$CH_2CH=CH_2$	=O	---	H	H	A	CH_3	---
421	o-CF_3-C_6H_4	$CH_2CH=CH_2$	=O	---	H	H	A	CH_3	---
422	$(C_2H_5)_2CHNH$	$CH_2CH=CH_2$	=O	---	H	H	A	CH_3	---
423	$C_4H_9(C_2H_5)N$	$CH_2CH=CH_2$	H	H	H	H	A	CH_3	---
424	$CH_3OCH_2CH(C_2H_5)NH$	$CH_2CH=CH_2$	H	H	H	H	A	CH_3	---
425	$(CH_3O(CH_2)_2)_2N$	$CH_2CH=CH_2$	H	H	H	H	A	CH_3	---
426	$(CH_3)_2NCH_2CH(C_3H_7)NH$	$CH_2CH=CH_2$	H	H	H	H	A	CH_3	---
427	o-CF_3-C_6H_4	$CH_2CH=CH_2$	H	H	H	H	A	CH_3	---
428	$(C_2H_5)_2CHNH$	$CH_2CH=CH_2$	H	H	H	H	A	CH_3	---
429	$C_4H_9(C_2H_5)N$	$CH_2CH=CH_2$	=O	---	$CH_2CH=CH_2$	H	A	CH_3	---
430	$CH_3OCH_2CH(C_2H_5)NH$	$CH_2CH=CH_2$	=O	---	$CH_2CH=CH_2$	H	A	CH_3	---
431	$(CH_3O(CH_2)_2)_2N$	$CH_2CH=CH_2$	=O	---	$CH_2CH=CH_2$	H	A	CH_3	---
432	$(CH_3)_2NCH_2CH(C_3H_7)NH$	$CH_2CH=CH_2$	=O	---	$CH_2CH=CH_2$	H	A	CH_3	---
433	o-CF_3-C_6H_4	CH_3	=O	---	$CH_2CH=CH_2$	H	A	CH_3	---
434	$(C_2H_5)_2CHNH$	$CH_2CH=CH_2$	=O	---	$CH_2CH=CH_2$	H	A	CH_3	---
435	$C_4H_9(C_2H_5)N$	$CH_2CH=CH_2$	H	H	$CH_2CH=CH_2$	H	A	CH_3	---
436	$CH_3OCH_2CH(C_2H_5)NH$	$CH_2CH=CH_2$	H	H	$CH_2CH=CH_2$	H	A	CH_3	---
437	$(CH_3O(CH_2)_2)_2N$	$CH_2CH=CH_2$	H	H	$CH_2CH=CH_2$	H	A	CH_3	---
438	$(CH_3)_2NCH_2CH(C_3H_7)NH$	$CH_2CH=CH_2$	H	H	$CH_2CH=CH_2$	H	A	CH_3	---
439	o-CF_3-C_6H_4	$CH_2CH=CH_2$	H	H	$CH_2CH=CH_2$	H	A	CH_3	---
440	$(C_2H_5)_2CHNH$	$CH_2CH=CH_2$	H	H	$CH_2CH=CH_2$	H	A	CH_3	---
441	$C_4H_9(C_2H_5)N$	H	CH_3	CH_3	H	H	A	CH_3	---
442	$CH_3OCH_2CH(C_2H_5)NH$	H	CH_3	CH_3	H	H	A	CH_3	---

443	$(CH_3O(CH_2)_2)_2N$	H	CH_3	CH_3	H	H	A	CH_3	---
444	$(CH_3)_2NCH_2CH(C_3H_7)NH$	H	CH_3	CH_3	H	H	A	CH_3	---
445	o-CF_3-C_6H_4	H	CH_3	CH_3	H	H	A	CH_3	---
446	$(C_2H_5)_2CHNH$	H	CH_3	CH_3	H	H	A	CH_3	---
447	$C_4H_9(C_2H_5)N$	H	=O	---	CH_3	CH_3	A	CH_3	---
448	$CH_3OCH_2CH(C_2H_5)NH$	H	=O	---	CH_3	CH_3	A	CH_3	---
449	$(CH_3O(CH_2)_2)_2N$	H	=O	---	CH_3	CH_3	A	CH_3	---
450	$(CH_3)_2NCH_2CH(C_3H_7)NH$	H	=O	---	CH_3	CH_3	A	CH_3	---
451	o-CF_3-C_6H_4	H	=O	---	CH_3	CH_3	A	CH_3	---
452	$(C_2H_5)_2CHNH$	H	=O	---	CH_3	CH_3	A	CH_3	---
453	$C_4H_9(C_2H_5)N$	H	H	H	CH_3	CH_3	A	CH_3	---
454	$CH_3OCH_2CH(C_2H_5)NH$	H	H	H	CH_3	CH_3	A	CH_3	---
455	$(CH_3O(CH_2)_2)_2N$	H	H	H	CH_3	CH_3	A	CH_3	---
456	$(CH_3)_2NCH_2CH(C_3H_7)NH$	H	H	H	CH_3	CH_3	A	CH_3	---
457	o-CF_3-C_6H_4	H	H	H	CH_3	CH_3	A	CH_3	---
458	$(C_2H_5)_2CHNH$	H	H	H	CH_3	CH_3	A	CH_3	---
459	$C_4H_9(C_2H_5)N$	H	=O	---	H	H	A	H	---
460	$CH_3OCH_2CH(C_2H_5)NH$	H	=O	---	H	H	A	H	---
461	$(CH_3O(CH_2)_2)_2N$	H	=O	---	H	H	A	H	---
462	$(CH_3)_2NCH_2CH(C_3H_7)NH$	H	=O	---	H	H	A	H	---
463	o-CF_3-C_6H_4	H	=O	---	H	H	A	H	---
464	$(C_2H_5)_2CHNH$	H	=O	---	H	H	A	H	---
465	$C_4H_9(C_2H_5)N$	H	H	H	H	H	A	H	---
466	$CH_3OCH_2CH(C_2H_5)NH$	H	H	H	H	H	A	H	---
467	$(CH_3O(CH_2)_2)_2N$	H	H	H	H	H	A	H	---

468	$(CH_3)_2NCH_2CH(C_3H_7)NH$	H	H	H	H	H	A	H	---
469	o-CF_3-C_6H_4	H	H	H	H	H	A	H	---
470	$(C_2H_5)_2CHNH$	H	H	H	H	H	A	H	---
471	$C_4H_9(C_2H_5)N$	H	=O	---	H	H	A	CN	---
472	$CH_3OCH_2CH(C_2H_5)NH$	H	=O	---	H	H	A	CN	---
473	$(CH_3O(CH_2)_2)_2N$	H	=O	---	H	H	A	CN	---
474	$(CH_3)_2NCH_2CH(C_3H_7)NH$	H	=O	---	H	H	A	CN	---
475	o-CF_3-C_6H_4	H	=O	---	H	H	A	CN	---
476	$(C_2H_5)_2CHNH$	H	=O	---	H	H	A	CN	---
477	$C_4H_9(C_2H_5)N$	H	H	H	H	H	A	CN	---
478	$CH_3OCH_2CH(C_2H_5)NH$	H	H	H	H	H	A	CN	---
479	$(CH_3O(CH_2)_2)_2N$	H	H	H	H	H	A	CN	---
480	$(CH_3)_2NCH_2CH(C_3H_7)NH$	H	H	H	H	H	A	CN	---
481	o-CF_3-C_6H_4	H	H	H	H	H	A	CN	---
482	$(C_2H_5)_2CHNH$	H	H	H	H	H	A	CN	---
483	2-morpholinyl	H	H	H	H	H	A	CH_3	---
484	2-morpholinyl	H	=O	---	H	H	B	CH_3	---
485	2-morpholinyl	H	=O	---	H	H	C	CH_3	---
486	2-morpholinyl	H	=O	---	H	H	D	CH_3	---
487	2-morpholinyl	H	=O	---	H	H	E	CH_3	---
488	2-morpholinyl	H	=O	---	H	H	F	CH_3	---
489	2-morpholinyl	H	=O	---	H	H	G	CH_3	---
490	2-morpholinyl	H	=O	---	H	H	J	CH_3	---
491	2-morpholinyl	H	H	H	H	H	B	CH_3	---
492	2-morpholinyl	H	H	H	H	H	C	CH_3	---

493	2-morpholinyl	H	H	H	H	H	D	CH_3	---
494	2-morpholinyl	H	H	H	H	H	E	CH_3	---
495	2-morpholinyl	H	H	H	H	H	F	CH_3	---
496	2-morpholinyl	H	H	H	H	H	G	CH_3	---
497	2-morpholinyl	H	H	H	H	H	J	CH_3	---
498	$C_4H_9(C_2H_5)N$	H	=NH	---	H	H	A	CH_3	---
499	$C_4H_9(C_2H_5)N$	H	=NH	---	H	H	C	CH_3	---
500	$C_4H_9(C_2H_5)N$	H	$=NC_4H_9$	---	H	H	A	CH_3	---

Key: (a) R^9 group codes: A =  ; B =  ; C =  ; D =  ;

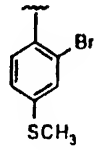
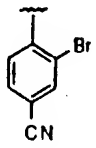
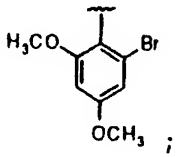
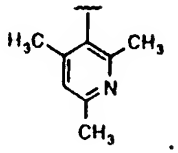
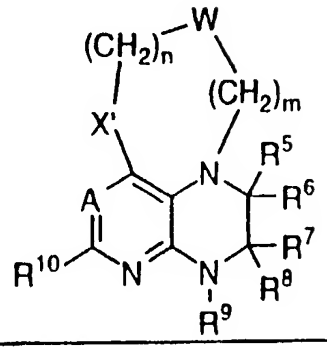
E =  ; F =  ; G =  ; J = 

Table III.



Ex. No.	A	X'	n	W	m	R^5	R^6	R^7	R^8	R^{9a}	R^{10}	m.p.
501	N	C_4H_9N	0	C=O	1	=O	---	H	H	A	CH_3	207-208
502	N	C_4H_9N	0	C=O	1	=O	---	H	H	B	CH_3	---
503	N	C_4H_9N	0	C=O	1	=O	---	H	H	C	CH_3	---
504	N	C_4H_9N	0	C=O	1	=O	---	H	H	D	CH_3	---
505	N	C_4H_9N	0	C=O	1	=O	---	H	H	E	CH_3	---
506	N	C_4H_9N	0	C=O	1	=O	---	H	H	F	CH_3	---
507	N	C_4H_9N	0	C=O	1	=O	---	H	H	G	CH_3	---
508	N	C_4H_9N	0	C=O	1	=O	---	H	H	J	CH_3	---
509	N	$(C_2H_5)_2CHN$	0	C=O	1	=O	---	H	H	A	CH_3	---
510	N	$(C_2H_5)_2CHN$	0	C=O	1	=O	---	H	H	B	CH_3	---
511	N	$(C_2H_5)_2CHN$	0	C=O	1	=O	---	H	H	C	CH_3	---
512	N	$CH_3OCH_2CH(C_2H_5)N$	0	C=O	1	=O	---	H	H	A	CH_3	---
513	N	$CH_3OCH_2CH(C_2H_5)N$	0	C=O	1	=O	---	H	H	B	CH_3	---
514	N	$CH_3OCH_2CH(C_2H_5)N$	0	C=O	1	=O	---	H	H	C	CH_3	---
515	N	$C_4H_9CH(C_2H_5)N$	0	C=O	1	=O	---	H	H	A	CH_3	---
516	N	$C_4H_9CH(C_2H_5)N$	0	C=O	1	=O	---	H	H	B	CH_3	---
517	N	$C_4H_9CH(C_2H_5)N$	0	C=O	1	=O	---	H	H	C	CH_3	---

518	N	C_4H_9N	0	CH_2	1	H	H	H	H	A	CH_3	---
519	N	C_4H_9N	0	CH_2	1	H	H	H	H	B	CH_3	---
520	N	C_4H_9N	0	CH_2	1	H	H	H	H	C	CH_3	---
521	N	$(C_2H_5)_2CHN$	0	CH_2	1	H	H	H	H	A	CH_3	---
522	N	$(C_2H_5)_2CHN$	0	CH_2	1	H	H	H	H	B	CH_3	---
523	N	$(C_2H_5)_2CHN$	0	CH_2	1	H	H	H	H	C	CH_3	---
524	N	$CH_3OCH_2CH(C_2H_5)N$	0	CH_2	1	H	H	H	H	A	CH_3	---
525	N	$CH_3OCH_2CH(C_2H_5)N$	0	CH_2	1	H	H	H	H	B	CH_3	---
526	N	$CH_3OCH_2CH(C_2H_5)N$	0	CH_2	1	H	H	H	H	C	CH_3	---
527	N	$C_4H_9CH(C_2H_5)N$	0	CH_2	1	H	H	H	H	A	CH_3	---
528	N	$C_4H_9CH(C_2H_5)N$	0	CH_2	1	H	H	H	H	B	CH_3	---
529	N	$C_4H_9CH(C_2H_5)N$	0	CH_2	1	H	H	H	H	C	CH_3	---
530	N	C_4H_9N	1	CH_2	1	=O	---	H	H	A	CH_3	---
531	N	C_4H_9N	1	CH_2	1	=O	---	H	H	B	CH_3	---
532	N	C_4H_9N	1	CH_2	1	=O	---	H	H	C	CH_3	---
533	N	$(C_2H_5)_2CHN$	1	CH_2	1	=O	---	H	H	A	CH_3	---
534	N	$(C_2H_5)_2CHN$	1	CH_2	1	=O	---	H	H	B	CH_3	---
535	N	$(C_2H_5)_2CHN$	1	CH_2	1	=O	---	H	H	C	CH_3	---
536	N	$CH_3OCH_2CH(C_2H_5)N$	1	CH_2	1	=O	---	H	H	A	CH_3	---
537	N	$CH_3OCH_2CH(C_2H_5)N$	1	CH_2	1	=O	---	H	H	B	CH_3	---
538	N	$CH_3OCH_2CH(C_2H_5)N$	1	CH_2	1	=O	---	H	H	C	CH_3	---
539	N	$C_4H_9CH(C_2H_5)N$	1	CH_2	1	=O	---	H	H	A	CH_3	---
540	N	$C_4H_9CH(C_2H_5)N$	1	CH_2	1	=O	---	H	H	B	CH_3	---
541	N	$C_4H_9CH(C_2H_5)N$	1	CH_2	1	=O	---	H	H	C	CH_3	---
542	N	C_4H_9N	1	CH_2	1	H	H	H	H	A	CH_3	---
543	N	C_4H_9N	1	CH_2	1	H	H	H	H	B	CH_3	---
544	N	C_4H_9N	1	CH_2	1	H	H	H	H	C	CH_3	---

545	N	$(C_2H_5)_2CHN$	1	CH_2	1	H	H	H	H	A	CH_3	---
546	N	$(C_2H_5)_2CHN$	1	CH_2	1	H	H	H	H	B	CH_3	---
547	N	$(C_2H_5)_2CHN$	1	CH_2	1	H	H	H	H	C	CH_3	---
548	N	$CH_3OCH_2CH(C_2H_5)N$	1	CH_2	1	H	H	H	H	A	CH_3	---
549	N	$CH_3OCH_2CH(C_2H_5)N$	1	CH_2	1	H	H	H	H	B	CH_3	---
550	N	$CH_3OCH_2CH(C_2H_5)N$	1	CH_2	1	H	H	H	H	C	CH_3	---
551	N	$C_4H_9CH(C_2H_5)N$	1	CH_2	1	H	H	H	H	A	CH_3	---
552	N	$C_4H_9CH(C_2H_5)N$	1	CH_2	1	H	H	H	H	B	CH_3	---
553	N	$C_4H_9CH(C_2H_5)N$	1	CH_2	1	H	H	H	H	C	CH_3	---
554	N	C_4H_9N	0	CH_2	1	=O	---	H	H	A	CH_3	---
555	N	C_4H_9N	0	CH_2	1	=O	---	H	H	B	CH_3	---
556	N	C_4H_9N	0	CH_2	1	=O	---	H	H	C	CH_3	---
557	N	$(C_2H_5)_2CHN$	0	CH_2	1	=O	---	H	H	A	CH_3	---
558	N	$(C_2H_5)_2CHN$	0	CH_2	1	=O	---	H	H	B	CH_3	---
559	N	$(C_2H_5)_2CHN$	0	CH_2	1	=O	---	H	H	C	CH_3	---
560	N	$CH_3OCH_2CH(C_2H_5)N$	0	CH_2	1	=O	---	H	H	A	CH_3	---
561	N	$CH_3OCH_2CH(C_2H_5)N$	0	CH_2	1	=O	---	H	H	B	CH_3	---
562	N	$CH_3OCH_2CH(C_2H_5)N$	0	CH_2	1	=O	---	H	H	C	CH_3	---
563	N	$C_4H_9CH(C_2H_5)N$	0	CH_2	1	=O	---	H	H	A	CH_3	---
564	N	$C_4H_9CH(C_2H_5)N$	0	CH_2	1	=O	---	H	H	B	CH_3	---
565	N	$C_4H_9CH(C_2H_5)N$	0	CH_2	1	=O	---	H	H	C	CH_3	---
566	N	C_4H_9N	1	C=O	1	=O	---	H	H	A	CH_3	---
567	N	C_4H_9N	1	C=O	1	=O	---	H	H	B	CH_3	---
568	N	C_4H_9N	1	C=O	1	=O	---	H	H	C	CH_3	---
569	N	$(C_2H_5)_2CHN$	1	C=O	1	=O	---	H	H	A	CH_3	---
570	N	$(C_2H_5)_2CHN$	1	C=O	1	=O	---	H	H	B	CH_3	---
571	N	$(C_2H_5)_2CHN$	1	C=O	1	=O	---	H	H	C	CH_3	---

572	N	$CH_3OCH_2CH(C_2H_5)N$	1	C=O	1	=O	---	H	H	A	CH_3	---
573	N	$CH_3OCH_2CH(C_2H_5)N$	1	C=O	1	=O	---	H	H	B	CH_3	---
574	N	$CH_3OCH_2CH(C_2H_5)N$	1	C=O	1	=O	---	H	H	C	CH_3	---
575	N	$C_4H_9CH(C_2H_5)N$	1	C=O	1	=O	---	H	H	A	CH_3	---
576	N	$C_4H_9CH(C_2H_5)N$	1	C=O	1	=O	---	H	H	B	CH_3	---
577	N	$C_4H_9CH(C_2H_5)N$	1	C=O	1	=O	---	H	H	C	CH_3	---
578	N	C_4H_9N	1	C=O	0	H	H	H	H	A	CH_3	---
579	N	C_4H_9N	1	C=O	0	H	H	H	H	B	CH_3	---
580	N	C_4H_9N	1	C=O	0	H	H	H	H	C	CH_3	---
581	N	$(C_2H_5)_2CHN$	1	C=O	0	H	H	H	H	A	CH_3	---
582	N	$(C_2H_5)_2CHN$	1	C=O	0	H	H	H	H	B	CH_3	---
583	N	$(C_2H_5)_2CHN$	1	C=O	0	H	H	H	H	C	CH_3	---
584	N	$CH_3OCH_2CH(C_2H_5)N$	1	C=O	0	H	H	H	H	A	CH_3	---
585	N	$CH_3OCH_2CH(C_2H_5)N$	1	C=O	0	H	H	H	H	B	CH_3	---
586	N	$CH_3OCH_2CH(C_2H_5)N$	1	C=O	0	H	H	H	H	C	CH_3	---
587	N	$C_4H_9CH(C_2H_5)N$	1	C=O	0	H	H	H	H	A	CH_3	---
588	N	$C_4H_9CH(C_2H_5)N$	1	C=O	0	H	H	H	H	B	CH_3	---
589	N	$C_4H_9CH(C_2H_5)N$	1	C=O	0	H	H	H	H	C	CH_3	---
590	N	C_4H_9N	0	C=O	0	H	H	H	H	A	CH_3	---
591	N	C_4H_9N	0	C=O	0	H	H	H	H	B	CH_3	---
592	N	C_4H_9N	0	C=O	0	H	H	H	H	C	CH_3	---
593	N	$(C_2H_5)_2CHN$	0	C=O	0	H	H	H	H	A	CH_3	---
594	N	$(C_2H_5)_2CHN$	0	C=O	0	H	H	H	H	B	CH_3	---
595	N	$(C_2H_5)_2CHN$	0	C=O	0	H	H	H	H	C	CH_3	---
596	N	$CH_3OCH_2CH(C_2H_5)N$	0	C=O	0	H	H	H	H	A	CH_3	---
597	N	$CH_3OCH_2CH(C_2H_5)N$	0	C=O	0	H	H	H	H	B	CH_3	---
598	N	$CH_3OCH_2CH(C_2H_5)N$	0	C=O	0	H	H	H	H	C	CH_3	---

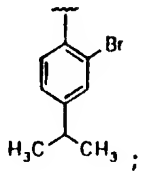
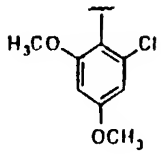
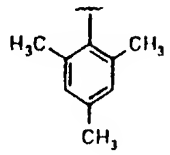
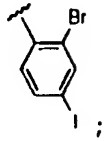
599	N	$C_4H_9CH(C_2H_5)N$	0	C=O	0	H	H	H	H	A	CH_3	---
600	N	$C_4H_9CH(C_2H_5)N$	0	C=O	0	H	H	H	H	B	CH_3	---
601	N	$C_4H_9CH(C_2H_5)N$	0	C=O	0	H	H	H	H	C	CH_3	---
602	CH	C_4H_9N	0	C=O	1	=O	---	H	H	A	CH_3	---
603	CH	C_4H_9N	0	C=O	1	=O	---	H	H	B	CH_3	---
604	CH	C_4H_9N	0	C=O	1	=O	---	H	H	C	CH_3	---
605	CH	$(C_2H_5)_2CHN$	0	C=O	1	=O	---	H	H	A	CH_3	---
606	CH	$(C_2H_5)_2CHN$	0	C=O	1	=O	---	H	H	B	CH_3	---
607	CH	$(C_2H_5)_2CHN$	0	C=O	1	=O	---	H	H	C	CH_3	---
608	CH	$CH_3OCH_2CH(C_2H_5)N$	0	C=O	1	=O	---	H	H	A	CH_3	---
609	CH	$CH_3OCH_2CH(C_2H_5)N$	0	C=O	1	=O	---	H	H	B	CH_3	---
610	CH	$CH_3OCH_2CH(C_2H_5)N$	0	C=O	1	=O	---	H	H	C	CH_3	---
611	CH	$C_4H_9CH(C_2H_5)N$	0	C=O	1	=O	---	H	H	A	CH_3	---
612	CH	$C_4H_9CH(C_2H_5)N$	0	C=O	1	=O	---	H	H	B	CH_3	---
613	CH	$C_4H_9CH(C_2H_5)N$	0	C=O	1	=O	---	H	H	C	CH_3	---
614	CH	C_4H_9N	0	CH_2	1	H	H	H	H	A	CH_3	---
615	CH	C_4H_9N	0	CH_2	1	H	H	H	H	B	CH_3	---
616	CH	C_4H_9N	0	CH_2	1	H	H	H	H	C	CH_3	---
617	CH	$(C_2H_5)_2CHN$	0	CH_2	1	H	H	H	H	A	CH_3	---
618	CH	$(C_2H_5)_2CHN$	0	CH_2	1	H	H	H	H	B	CH_3	---
619	CH	$(C_2H_5)_2CHN$	0	CH_2	1	H	H	H	H	C	CH_3	---
620	CH	$CH_3OCH_2CH(C_2H_5)N$	0	CH_2	1	H	H	H	H	A	CH_3	---
621	CH	$CH_3OCH_2CH(C_2H_5)N$	0	CH_2	1	H	H	H	H	B	CH_3	---
622	CH	$CH_3OCH_2CH(C_2H_5)N$	0	CH_2	1	H	H	H	H	C	CH_3	---
623	CH	$C_4H_9CH(C_2H_5)N$	0	CH_2	1	H	H	H	H	A	CH_3	---
624	CH	$C_4H_9CH(C_2H_5)N$	0	CH_2	1	H	H	H	H	B	CH_3	---
625	CH	$C_4H_9CH(C_2H_5)N$	0	CH_2	1	H	H	H	H	C	CH_3	---

626	CH	C_4H_9N	1	CH_2	1	=O	---	H	H	A	CH_3	---
627	CH	C_4H_9N	1	CH_2	1	=O	---	H	H	B	CH_3	---
628	CH	C_4H_9N	1	CH_2	1	=O	---	H	H	C	CH_3	---
629	CH	$(C_2H_5)_2CHN$	1	CH_2	1	=O	---	H	H	A	CH_3	---
630	CH	$(C_2H_5)_2CHN$	1	CH_2	1	=O	---	H	H	B	CH_3	---
631	CH	$(C_2H_5)_2CHN$	1	CH_2	1	=O	---	H	H	C	CH_3	---
632	CH	$CH_3OCH_2CH(C_2H_5)N$	1	CH_2	1	=O	---	H	H	A	CH_3	---
633	CH	$CH_3OCH_2CH(C_2H_5)N$	1	CH_2	1	=O	---	H	H	B	CH_3	---
634	CH	$CH_3OCH_2CH(C_2H_5)N$	1	CH_2	1	=O	---	H	H	C	CH_3	---
635	CH	$C_4H_9CH(C_2H_5)N$	1	CH_2	1	=O	---	H	H	A	CH_3	---
636	CH	$C_4H_9CH(C_2H_5)N$	1	CH_2	1	=O	---	H	H	B	CH_3	---
637	CH	$C_4H_9CH(C_2H_5)N$	1	CH_2	1	=O	---	H	H	C	CH_3	---
638	CH	C_4H_9N	1	CH_2	1	H	H	H	H	A	CH_3	---
639	CH	C_4H_9N	1	CH_2	1	H	H	H	H	B	CH_3	---
640	CH	C_4H_9N	1	CH_2	1	H	H	H	H	C	CH_3	---
641	CH	$(C_2H_5)_2CHN$	1	CH_2	1	H	H	H	H	A	CH_3	---
642	CH	$(C_2H_5)_2CHN$	1	CH_2	1	H	H	H	H	B	CH_3	---
643	CH	$(C_2H_5)_2CHN$	1	CH_2	1	H	H	H	H	C	CH_3	---
644	CH	$CH_3OCH_2CH(C_2H_5)N$	1	CH_2	1	H	H	H	H	A	CH_3	---
645	CH	$CH_3OCH_2CH(C_2H_5)N$	1	CH_2	1	H	H	H	H	B	CH_3	---
646	CH	$CH_3OCH_2CH(C_2H_5)N$	1	CH_2	1	H	H	H	H	C	CH_3	---
647	CH	$C_4H_9CH(C_2H_5)N$	1	CH_2	1	H	H	H	H	A	CH_3	---
648	CH	$C_4H_9CH(C_2H_5)N$	1	CH_2	1	H	H	H	H	B	CH_3	---
649	CH	$C_4H_9CH(C_2H_5)N$	1	CH_2	1	H	H	H	H	C	CH_3	---
650	CH	C_4H_9N	0	CH_2	1	=O	---	H	H	A	CH_3	---
651	CH	C_4H_9N	0	CH_2	1	=O	---	H	H	B	CH_3	---
652	CH	C_4H_9N	0	CH_2	1	=O	---	H	H	C	CH_3	---

653	CH	$(C_2H_5)_2CHN$	0	CH_2	1	=O	---	H	H	A	CH_3	---
654	CH	$(C_2H_5)_2CHN$	0	CH_2	1	=O	---	H	H	B	CH_3	---
655	CH	$(C_2H_5)_2CHN$	0	CH_2	1	=O	---	H	H	C	CH_3	---
656	CH	$CH_3OCH_2CH(C_2H_5)N$	0	CH_2	1	=O	---	H	H	A	CH_3	---
657	CH	$CH_3OCH_2CH(C_2H_5)N$	0	CH_2	1	=O	---	H	H	B	CH_3	---
658	CH	$CH_3OCH_2CH(C_2H_5)N$	0	CH_2	1	=O	---	H	H	C	CH_3	---
659	CH	$C_4H_9CH(C_2H_5)N$	0	CH_2	1	=O	---	H	H	A	CH_3	---
660	CH	$C_4H_9CH(C_2H_5)N$	0	CH_2	1	=O	---	H	H	B	CH_3	---
661	CH	$C_4H_9CH(C_2H_5)N$	0	CH_2	1	=O	---	H	H	C	CH_3	---
662	CH	C_4H_9N	1	C=O	1	=O	---	H	H	A	CH_3	---
663	CH	C_4H_9N	1	C=O	1	=O	---	H	H	B	CH_3	---
664	CH	C_4H_9N	1	C=O	1	=O	---	H	H	C	CH_3	---
665	CH	$(C_2H_5)_2CHN$	1	C=O	1	=O	---	H	H	A	CH_3	---
666	CH	$(C_2H_5)_2CHN$	1	C=O	1	=O	---	H	H	B	CH_3	---
667	CH	$(C_2H_5)_2CHN$	1	C=O	1	=O	---	H	H	C	CH_3	---
668	CH	$CH_3OCH_2CH(C_2H_5)N$	1	C=O	1	=O	---	H	H	A	CH_3	---
669	CH	$CH_3OCH_2CH(C_2H_5)N$	1	C=O	1	=O	---	H	H	B	CH_3	---
670	CH	$CH_3OCH_2CH(C_2H_5)N$	1	C=O	1	=O	---	H	H	C	CH_3	---
671	CH	$C_4H_9CH(C_2H_5)N$	1	C=O	1	=O	---	H	H	A	CH_3	---
672	CH	$C_4H_9CH(C_2H_5)N$	1	C=O	1	=O	---	H	H	B	CH_3	---
673	CH	$C_4H_9CH(C_2H_5)N$	1	C=O	1	=O	---	H	H	C	CH_3	---
674	CH	C_4H_9N	1	C=O	0	H	H	H	H	A	CH_3	---
675	CH	C_4H_9N	1	C=O	0	H	H	H	H	B	CH_3	---
676	CH	C_4H_9N	1	C=O	0	H	H	H	H	C	CH_3	---
677	CH	$(C_2H_5)_2CHN$	1	C=O	0	H	H	H	H	A	CH_3	---
678	CH	$(C_2H_5)_2CHN$	1	C=O	0	H	H	H	H	B	CH_3	---
679	CH	$(C_2H_5)_2CHN$	1	C=O	0	H	H	H	H	C	CH_3	---

680	CH	$CH_3OCH_2CH(C_2H_5)N$	1	C=O	0	H	H	H	H	A	CH_3	---
681	CH	$CH_3OCH_2CH(C_2H_5)N$	1	C=O	0	H	H	H	H	B	CH_3	---
682	CH	$CH_3OCH_2CH(C_2H_5)N$	1	C=O	0	H	H	H	H	C	CH_3	---
683	CH	$C_4H_9CH(C_2H_5)N$	1	C=O	0	H	H	H	H	A	CH_3	---
684	CH	$C_4H_9CH(C_2H_5)N$	1	C=O	0	H	H	H	H	B	CH_3	---
685	CH	$C_4H_9CH(C_2H_5)N$	1	C=O	0	H	H	H	H	C	CH_3	---
686	CH	C_4H_9N	0	C=O	0	H	H	H	H	A	CH_3	---
687	CH	C_4H_9N	0	C=O	0	H	H	H	H	B	CH_3	---
688	CH	C_4H_9N	0	C=O	0	H	H	H	H	C	CH_3	---
689	CH	$(C_2H_5)_2CHN$	0	C=O	0	H	H	H	H	A	CH_3	---
690	CH	$(C_2H_5)_2CHN$	0	C=O	0	H	H	H	H	B	CH_3	---
691	CH	$(C_2H_5)_2CHN$	0	C=O	0	H	H	H	H	C	CH_3	---
692	CH	$CH_3OCH_2CH(C_2H_5)N$	0	C=O	0	H	H	H	H	A	CH_3	---
693	CH	$CH_3OCH_2CH(C_2H_5)N$	0	C=O	0	H	H	H	H	B	CH_3	---
694	CH	$CH_3OCH_2CH(C_2H_5)N$	0	C=O	0	H	H	H	H	C	CH_3	---
695	CH	$C_4H_9CH(C_2H_5)N$	0	C=O	0	H	H	H	H	A	CH_3	---
696	CH	$C_4H_9CH(C_2H_5)N$	0	C=O	0	H	H	H	H	B	CH_3	---
697	CH	$C_4H_9CH(C_2H_5)N$	0	C=O	0	H	H	H	H	C	CH_3	---
698	N	$[C_2H_5OC(=O)]_2C$	0	CH_2	1	=O	---	H	H	A	CH_3	---
699	N	$[C_2H_5OC(=O)]_2C$	0	CH_2	1	=O	---	H	H	B	CH_3	---
700	N	$[C_2H_5OC(=O)]_2C$	0	CH_2	1	=O	---	H	H	C	CH_3	---
701	N	$[C_2H_5OC(=O)]_2C$	0	CH_2	1	H	H	H	H	A	CH_3	---
702	N	$[C_2H_5OC(=O)]_2C$	0	CH_2	1	H	H	H	H	B	CH_3	---
703	N	$[C_2H_5OC(=O)]_2C$	0	CH_2	1	H	H	H	H	C	CH_3	---
704	N	$(CH_3OCH_2)_2C$	0	CH_2	1	H	H	H	H	A	CH_3	---
705	N	$(CH_3OCH_2)_2C$	0	CH_2	1	H	H	H	H	B	CH_3	---
706	N	$(CH_3OCH_2)_2C$	0	CH_2	1	H	H	H	H	C	CH_3	---

707	N	$(NC)_2C$	0	CH_2	1	=O	---	H	H	A	CH_3	---
708	N	$(NC)_2C$	0	CH_2	1	=O	---	H	H	B	CH_3	---
709	N	$(NC)_2C$	0	CH_2	1	=O	---	H	H	C	CH_3	---
710	N	$[C_2H_5OC(=O)]_2C$	1	CH_2	1	=O	---	H	H	A	CH_3	---
711	N	$[C_2H_5OC(=O)]_2C$	1	CH_2	1	=O	---	H	H	B	CH_3	---
712	N	$[C_2H_5OC(=O)]_2C$	1	CH_2	1	=O	---	H	H	C	CH_3	---
713	N	$[C_2H_5OC(=O)]_2C$	1	CH_2	1	H	H	H	H	A	CH_3	---
714	N	$[C_2H_5OC(=O)]_2C$	1	CH_2	1	H	H	H	H	B	CH_3	---
715	N	$[C_2H_5OC(=O)]_2C$	1	CH_2	1	H	H	H	H	C	CH_3	---
716	N	$(CH_3OCH_2)_2C$	1	CH_2	1	H	H	H	H	A	CH_3	---
717	N	$(CH_3OCH_2)_2C$	1	CH_2	1	H	H	H	H	B	CH_3	---
718	N	$(CH_3OCH_2)_2C$	1	CH_2	1	H	H	H	H	C	CH_3	---

Key: (a) R^9 group codes: A =  ; B =  ; C =  ; D =  ;

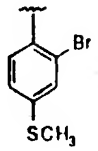
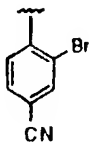
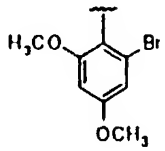
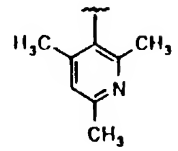
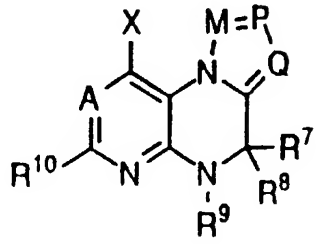
E =  ; F =  ; G =  ; J =  .

Table IV.



Ex. No.	A	X	M	P	Q	R^7	R^8	$R^{9\,a}$	R^{10}	m.p. b
719	N	$C_4H_9(C_2H_5)N$	N	N	N	H	H	A	CH_3	
720	N	$C_4H_9(C_2H_5)N$	N	N	N	H	H	B	CH_3	---
721	N	$C_4H_9(C_2H_5)N$	N	N	N	H	H	C	CH_3	---
722	N	$C_4H_9(C_2H_5)N$	N	N	N	H	H	D	CH_3	---
723	N	$C_4H_9(C_2H_5)N$	N	N	N	H	H	E	CH_3	---
724	N	$C_4H_9(C_2H_5)N$	N	N	N	H	H	F	CH_3	---
725	N	$C_4H_9(C_2H_5)N$	N	N	N	H	H	G	CH_3	---
726	N	$C_4H_9(C_2H_5)N$	N	N	N	H	H	J	CH_3	---
727	N	$(C_2H_5)_2N$	N	N	N	H	H	A	CH_3	---
728	N	$(C_2H_5)_2N$	N	N	N	H	H	B	CH_3	---
729	N	$(C_2H_5)_2N$	N	N	N	H	H	C	CH_3	---
730	N	$(C_2H_5)_2N$	N	N	N	H	H	D	CH_3	---
731	N	$(C_2H_5)_2N$	N	N	N	H	H	E	CH_3	---
732	N	$(C_2H_5)_2N$	N	N	N	H	H	F	CH_3	---
733	N	$(C_2H_5)_2N$	N	N	N	H	H	G	CH_3	---
734	N	$(C_2H_5)_2N$	N	N	N	H	H	J	CH_3	---
735	N	$CH_3OCH_2CH(C_2H_5)NH$	N	N	N	H	H	A	CH_3	---
736	N	$CH_3OCH_2CH(C_2H_5)NH$	N	N	N	H	H	B	CH_3	---

737	N	$CH_3OCH_2CH(C_2H_5)NH$	N	N	N	H	H	C	CH_3	---
738	N	$CH_3OCH_2CH(C_2H_5)NH$	N	N	N	H	H	D	CH_3	---
739	N	$CH_3OCH_2CH(C_2H_5)NH$	N	N	N	H	H	E	CH_3	---
740	N	$CH_3OCH_2CH(C_2H_5)NH$	N	N	N	H	H	F	CH_3	---
741	N	$CH_3OCH_2CH(C_2H_5)NH$	N	N	N	H	H	G	CH_3	---
742	N	$CH_3OCH_2CH(C_2H_5)NH$	N	N	N	H	H	J	CH_3	---
743	N	$[CH_3O(CH_2)_2]_2N$	N	N	N	H	H	A	CH_3	---
744	N	$[CH_3O(CH_2)_2]_2N$	N	N	N	H	H	B	CH_3	---
745	N	$[CH_3O(CH_2)_2]_2N$	N	N	N	H	H	C	CH_3	---
746	N	$[CH_3O(CH_2)_2]_2N$	N	N	N	H	H	D	CH_3	---
747	N	$[CH_3O(CH_2)_2]_2N$	N	N	N	H	H	E	CH_3	---
748	N	$[CH_3O(CH_2)_2]_2N$	N	N	N	H	H	F	CH_3	---
749	N	$[CH_3O(CH_2)_2]_2N$	N	N	N	H	H	G	CH_3	---
750	N	$[CH_3O(CH_2)_2]_2N$	N	N	N	H	H	J	CH_3	---
751	N	$(C_2H_5)_2CHNH$	N	N	N	H	H	A	CH_3	---
752	N	$(C_2H_5)_2CHNH$	N	N	N	H	H	B	CH_3	---
753	N	$(C_2H_5)_2CHNH$	N	N	N	H	H	C	CH_3	---
754	N	$(C_2H_5)_2CHNH$	N	N	N	H	H	D	CH_3	---
755	N	$(C_2H_5)_2CHNH$	N	N	N	H	H	E	CH_3	---
756	N	$(C_2H_5)_2CHNH$	N	N	N	H	H	F	CH_3	---
757	N	$(C_2H_5)_2CHNH$	N	N	N	H	H	G	CH_3	---
758	N	$(C_2H_5)_2CHNH$	N	N	N	H	H	J	CH_3	---
759	N	$C_4H_9(C_2H_5)N$	CH	CH	N	H	H	A	CH_3	---
760	N	$C_4H_9(C_2H_5)N$	CH	CH	N	H	H	B	CH_3	---
761	N	$C_4H_9(C_2H_5)N$	CH	CH	N	H	H	C	CH_3	---
762	N	$C_4H_9(C_2H_5)N$	CH	CH	N	H	H	D	CH_3	---
763	N	$C_4H_9(C_2H_5)N$	CH	CH	N	H	H	E	CH_3	---

764	N	$C_4H_9(C_2H_5)N$	CH	CH	N	H	H	F	CH_3	---
765	N	$C_4H_9(C_2H_5)N$	CH	CH	N	H	H	G	CH_3	---
766	N	$C_4H_9(C_2H_5)N$	CH	CH	N	H	H	J	CH_3	---
767	N	$(C_2H_5)_2N$	CH	CH	N	H	H	A	CH_3	---
768	N	$(C_2H_5)_2N$	CH	CH	N	H	H	B	CH_3	---
769	N	$(C_2H_5)_2N$	CH	CH	N	H	H	C	CH_3	---
770	N	$(C_2H_5)_2N$	CH	CH	N	H	H	D	CH_3	---
771	N	$(C_2H_5)_2N$	CH	CH	N	H	H	E	CH_3	---
772	N	$(C_2H_5)_2N$	CH	CH	N	H	H	F	CH_3	---
773	N	$(C_2H_5)_2N$	CH	CH	N	H	H	G	CH_3	---
774	N	$(C_2H_5)_2N$	CH	CH	N	H	H	J	CH_3	---
775	N	$CH_3OCH_2CH(C_2H_5)NH$	CH	CH	N	H	H	A	CH_3	---
776	N	$CH_3OCH_2CH(C_2H_5)NH$	CH	CH	N	H	H	B	CH_3	---
777	N	$CH_3OCH_2CH(C_2H_5)NH$	CH	CH	N	H	H	C	CH_3	---
778	N	$CH_3OCH_2CH(C_2H_5)NH$	CH	CH	N	H	H	D	CH_3	---
779	N	$CH_3OCH_2CH(C_2H_5)NH$	CH	CH	N	H	H	E	CH_3	---
780	N	$CH_3OCH_2CH(C_2H_5)NH$	CH	CH	N	H	H	F	CH_3	---
781	N	$CH_3OCH_2CH(C_2H_5)NH$	CH	CH	N	H	H	G	CH_3	---
782	N	$CH_3OCH_2CH(C_2H_5)NH$	CH	CH	N	H	H	J	CH_3	---
783	N	$[CH_3O(CH_2)_2]_2N$	CH	CH	N	H	H	A	CH_3	---
784	N	$[CH_3O(CH_2)_2]_2N$	CH	CH	N	H	H	B	CH_3	---
785	N	$[CH_3O(CH_2)_2]_2N$	CH	CH	N	H	H	C	CH_3	---
786	N	$[CH_3O(CH_2)_2]_2N$	CH	CH	N	H	H	D	CH_3	---
787	N	$[CH_3O(CH_2)_2]_2N$	CH	CH	N	H	H	E	CH_3	---
788	N	$[CH_3O(CH_2)_2]_2N$	CH	CH	N	H	H	F	CH_3	---
789	N	$[CH_3O(CH_2)_2]_2N$	CH	CH	N	H	H	G	CH_3	---
790	N	$[CH_3O(CH_2)_2]_2N$	CH	CH	N	H	H	J	CH_3	---

791	N	$(C_2H_5)_2CHNH$	CH	CH	N	H	H	A	CH_3	---
792	N	$(C_2H_5)_2CHNH$	CH	CH	N	H	H	B	CH_3	---
793	N	$(C_2H_5)_2CHNH$	CH	CH	N	H	H	C	CH_3	---
794	N	$(C_2H_5)_2CHNH$	CH	CH	N	H	H	D	CH_3	---
795	N	$(C_2H_5)_2CHNH$	CH	CH	N	H	H	E	CH_3	---
796	N	$(C_2H_5)_2CHNH$	CH	CH	N	H	H	F	CH_3	---
797	N	$(C_2H_5)_2CHNH$	CH	CH	N	H	H	G	CH_3	---
798	N	$(C_2H_5)_2CHNH$	CH	CH	N	H	H	J	CH_3	---
799	N	$C_4H_9(C_2H_5)N$	CCH_3	CCH_3	N	H	H	A	CH_3	---
800	N	$C_4H_9(C_2H_5)N$	CCH_3	CCH_3	N	H	H	B	CH_3	---
801	N	$C_4H_9(C_2H_5)N$	CCH_3	CCH_3	N	H	H	C	CH_3	---
802	N	$C_4H_9(C_2H_5)N$	CCH_3	CCH_3	N	H	H	D	CH_3	---
803	N	$C_4H_9(C_2H_5)N$	CCH_3	CCH_3	N	H	H	E	CH_3	---
804	N	$C_4H_9(C_2H_5)N$	CCH_3	CCH_3	N	H	H	F	CH_3	---
805	N	$C_4H_9(C_2H_5)N$	CCH_3	CCH_3	N	H	H	G	CH_3	---
806	N	$C_4H_9(C_2H_5)N$	CCH_3	CCH_3	N	H	H	J	CH_3	---
807	N	$(C_2H_5)_2N$	CCH_3	CCH_3	N	H	H	A	CH_3	---
808	N	$(C_2H_5)_2N$	CCH_3	CCH_3	N	H	H	B	CH_3	---
809	N	$(C_2H_5)_2N$	CCH_3	CCH_3	N	H	H	C	CH_3	---
810	N	$(C_2H_5)_2N$	CCH_3	CCH_3	N	H	H	D	CH_3	---
811	N	$(C_2H_5)_2N$	CCH_3	CCH_3	N	H	H	E	CH_3	---
812	N	$(C_2H_5)_2N$	CCH_3	CCH_3	N	H	H	F	CH_3	---
813	N	$(C_2H_5)_2N$	CCH_3	CCH_3	N	H	H	G	CH_3	---
814	N	$(C_2H_5)_2N$	CCH_3	CCH_3	N	H	H	J	CH_3	---
815	N	$CH_3OCH_2CH(C_2H_5)NH$	CCH_3	CCH_3	N	H	H	A	CH_3	---
816	N	$CH_3OCH_2CH(C_2H_5)NH$	CCH_3	CCH_3	N	H	H	B	CH_3	---
817	N	$CH_3OCH_2CH(C_2H_5)NH$	CCH_3	CCH_3	N	H	H	C	CH_3	---

818	N	$CH_3OCH_2CH(C_2H_5)NH$	CCH_3	CCH_3	N	H	H	D	CH_3	---
819	N	$CH_3OCH_2CH(C_2H_5)NH$	CCH_3	CCH_3	N	H	H	E	CH_3	---
820	N	$CH_3OCH_2CH(C_2H_5)NH$	CCH_3	CCH_3	N	H	H	F	CH_3	---
821	N	$CH_3OCH_2CH(C_2H_5)NH$	CCH_3	CCH_3	N	H	H	G	CH_3	---
822	N	$CH_3OCH_2CH(C_2H_5)NH$	CCH_3	CCH_3	N	H	H	J	CH_3	---
823	N	$[CH_3O(CH_2)2]_2N$	CCH_3	CCH_3	N	H	H	A	CH_3	---
824	N	$[CH_3O(CH_2)2]_2N$	CCH_3	CCH_3	N	H	H	B	CH_3	---
825	N	$[CH_3O(CH_2)2]_2N$	CCH_3	CCH_3	N	H	H	C	CH_3	---
826	N	$[CH_3O(CH_2)2]_2N$	CCH_3	CCH_3	N	H	H	D	CH_3	---
827	N	$[CH_3O(CH_2)2]_2N$	CCH_3	CCH_3	N	H	H	E	CH_3	---
828	N	$[CH_3O(CH_2)2]_2N$	CCH_3	CCH_3	N	H	H	F	CH_3	---
829	N	$[CH_3O(CH_2)2]_2N$	CCH_3	CCH_3	N	H	H	G	CH_3	---
830	N	$[CH_3O(CH_2)2]_2N$	CCH_3	CCH_3	N	H	H	J	CH_3	---
831	N	$(C_2H_5)_2CHNH$	CCH_3	CCH_3	N	H	H	A	CH_3	---
832	N	$(C_2H_5)_2CHNH$	CCH_3	CCH_3	N	H	H	B	CH_3	---
833	N	$(C_2H_5)_2CHNH$	CCH_3	CCH_3	N	H	H	C	CH_3	---
834	N	$(C_2H_5)_2CHNH$	CCH_3	CCH_3	N	H	H	D	CH_3	---
835	N	$(C_2H_5)_2CHNH$	CCH_3	CCH_3	N	H	H	E	CH_3	---
836	N	$(C_2H_5)_2CHNH$	CCH_3	CCH_3	N	H	H	F	CH_3	---
837	N	$(C_2H_5)_2CHNH$	CCH_3	CCH_3	N	H	H	G	CH_3	---
838	N	$(C_2H_5)_2CHNH$	CCH_3	CCH_3	N	H	H	J	CH_3	---
839	CH	$C_4H_9(C_2H_5)N$	N	N	N	H	H	A	CH_3	---
840	CH	$C_4H_9(C_2H_5)N$	N	N	N	H	H	B	CH_3	---
841	CH	$C_4H_9(C_2H_5)N$	N	N	N	H	H	C	CH_3	---
842	CH	$C_4H_9(C_2H_5)N$	N	N	N	H	H	D	CH_3	---
843	CH	$C_4H_9(C_2H_5)N$	N	N	N	H	H	E	CH_3	---
844	CH	$C_4H_9(C_2H_5)N$	N	N	N	H	H	F	CH_3	---

845	CH	$C_4H_9(C_2H_5)N$	N	N	N	H	H	G	CH_3	---
846	CH	$C_4H_9(C_2H_5)N$	N	N	N	H	H	J	CH_3	---
847	CH	$(C_2H_5)_2N$	N	N	N	H	H	A	CH_3	---
848	CH	$(C_2H_5)_2N$	N	N	N	H	H	B	CH_3	---
849	CH	$(C_2H_5)_2N$	N	N	N	H	H	C	CH_3	---
850	CH	$(C_2H_5)_2N$	N	N	N	H	H	D	CH_3	---
851	CH	$(C_2H_5)_2N$	N	N	N	H	H	E	CH_3	---
852	CH	$(C_2H_5)_2N$	N	N	N	H	H	F	CH_3	---
853	CH	$(C_2H_5)_2N$	N	N	N	H	H	G	CH_3	---
854	CH	$(C_2H_5)_2N$	N	N	N	H	H	J	CH_3	---
855	CH	$CH_3OCH_2CH(C_2H_5)NH$	N	N	N	H	H	A	CH_3	---
856	CH	$CH_3OCH_2CH(C_2H_5)NH$	N	N	N	H	H	B	CH_3	---
857	CH	$CH_3OCH_2CH(C_2H_5)NH$	N	N	N	H	H	C	CH_3	---
858	CH	$CH_3OCH_2CH(C_2H_5)NH$	N	N	N	H	H	D	CH_3	---
859	CH	$CH_3OCH_2CH(C_2H_5)NH$	N	N	N	H	H	E	CH_3	---
860	CH	$CH_3OCH_2CH(C_2H_5)NH$	N	N	N	H	H	F	CH_3	---
861	CH	$CH_3OCH_2CH(C_2H_5)NH$	N	N	N	H	H	G	CH_3	---
862	CH	$CH_3OCH_2CH(C_2H_5)NH$	N	N	N	H	H	J	CH_3	---
863	CH	$[CH_3O(CH_2)_2]_2N$	N	N	N	H	H	A	CH_3	---
864	CH	$[CH_3O(CH_2)_2]_2N$	N	N	N	H	H	B	CH_3	---
865	CH	$[CH_3O(CH_2)_2]_2N$	N	N	N	H	H	C	CH_3	---
866	CH	$[CH_3O(CH_2)_2]_2N$	N	N	N	H	H	D	CH_3	---
867	CH	$[CH_3O(CH_2)_2]_2N$	N	N	N	H	H	E	CH_3	---
868	CH	$[CH_3O(CH_2)_2]_2N$	N	N	N	H	H	F	CH_3	---
869	CH	$[CH_3O(CH_2)_2]_2N$	N	N	N	H	H	G	CH_3	---
870	CH	$[CH_3O(CH_2)_2]_2N$	N	N	N	H	H	J	CH_3	---
871	CH	$(C_2H_5)_2CHNH$	N	N	N	H	H	A	CH_3	---

872	CH	$(C_2H_5)_2CHNH$	N	N	N	H	H	B	CH_3	---
873	CH	$(C_2H_5)_2CHNH$	N	N	N	H	H	C	CH_3	---
874	CH	$(C_2H_5)_2CHNH$	N	N	N	H	H	D	CH_3	---
875	CH	$(C_2H_5)_2CHNH$	N	N	N	H	H	E	CH_3	---
876	CH	$(C_2H_5)_2CHNH$	N	N	N	H	H	F	CH_3	---
877	CH	$(C_2H_5)_2CHNH$	N	N	N	H	H	G	CH_3	---
878	CH	$(C_2H_5)_2CHNH$	N	N	N	H	H	J	CH_3	---
879	CH	$C_4H_9(C_2H_5)N$	CH	CH	N	H	H	A	CH_3	---
880	CH	$C_4H_9(C_2H_5)N$	CH	CH	N	H	H	B	CH_3	---
881	CH	$C_4H_9(C_2H_5)N$	CH	CH	N	H	H	C	CH_3	---
882	CH	$C_4H_9(C_2H_5)N$	CH	CH	N	H	H	D	CH_3	---
883	CH	$C_4H_9(C_2H_5)N$	CH	CH	N	H	H	E	CH_3	---
884	CH	$C_4H_9(C_2H_5)N$	CH	CH	N	H	H	F	CH_3	---
885	CH	$C_4H_9(C_2H_5)N$	CH	CH	N	H	H	G	CH_3	---
886	CH	$C_4H_9(C_2H_5)N$	CH	CH	N	H	H	J	CH_3	---
887	CH	$(C_2H_5)_2N$	CH	CH	N	H	H	A	CH_3	---
888	CH	$(C_2H_5)_2N$	CH	CH	N	H	H	B	CH_3	---
889	CH	$(C_2H_5)_2N$	CH	CH	N	H	H	C	CH_3	---
890	CH	$(C_2H_5)_2N$	CH	CH	N	H	H	D	CH_3	---
891	CH	$(C_2H_5)_2N$	CH	CH	N	H	H	E	CH_3	---
892	CH	$(C_2H_5)_2N$	CH	CH	N	H	H	F	CH_3	---
893	CH	$(C_2H_5)_2N$	CH	CH	N	H	H	G	CH_3	---
894	CH	$(C_2H_5)_2N$	CH	CH	N	H	H	J	CH_3	---
895	CH	$CH_3OCH_2CH(C_2H_5)NH$	CH	CH	N	H	H	A	CH_3	---
896	CH	$CH_3OCH_2CH(C_2H_5)NH$	CH	CH	N	H	H	B	CH_3	---
897	CH	$CH_3OCH_2CH(C_2H_5)NH$	CH	CH	N	H	H	C	CH_3	---
898	CH	$CH_3OCH_2CH(C_2H_5)NH$	CH	CH	N	H	H	D	CH_3	---

899	CH	$CH_3OCH_2CH(C_2H_5)NH$	CH	CH	N	H	H	E	CH_3	---
900	CH	$CH_3OCH_2CH(C_2H_5)NH$	CH	CH	N	H	H	F	CH_3	---
901	CH	$CH_3OCH_2CH(C_2H_5)NH$	CH	CH	N	H	H	G	CH_3	---
902	CH	$CH_3OCH_2CH(C_2H_5)NH$	CH	CH	N	H	H	J	CH_3	---
903	CH	$[CH_3O(CH_2)_2]_2N$	CH	CH	N	H	H	A	CH_3	---
904	CH	$[CH_3O(CH_2)_2]_2N$	CH	CH	N	H	H	B	CH_3	---
905	CH	$[CH_3O(CH_2)_2]_2N$	CH	CH	N	H	H	C	CH_3	---
906	CH	$[CH_3O(CH_2)_2]_2N$	CH	CH	N	H	H	D	CH_3	---
907	CH	$[CH_3O(CH_2)_2]_2N$	CH	CH	N	H	H	E	CH_3	---
908	CH	$[CH_3O(CH_2)_2]_2N$	CH	CH	N	H	H	F	CH_3	---
909	CH	$[CH_3O(CH_2)_2]_2N$	CH	CH	N	H	H	G	CH_3	---
910	CH	$[CH_3O(CH_2)_2]_2N$	CH	CH	N	H	H	J	CH_3	---
911	CH	$(C_2H_5)_2CHNH$	CH	CH	N	H	H	A	CH_3	---
912	CH	$(C_2H_5)_2CHNH$	CH	CH	N	H	H	B	CH_3	---
913	CH	$(C_2H_5)_2CHNH$	CH	CH	N	H	H	C	CH_3	---
914	CH	$(C_2H_5)_2CHNH$	CH	CH	N	H	H	D	CH_3	---
915	CH	$(C_2H_5)_2CHNH$	CH	CH	N	H	H	E	CH_3	---
916	CH	$(C_2H_5)_2CHNH$	CH	CH	N	H	H	F	CH_3	---
917	CH	$(C_2H_5)_2CHNH$	CH	CH	N	H	H	G	CH_3	---
918	CH	$(C_2H_5)_2CHNH$	CH	CH	N	H	H	J	CH_3	---
919	CH	$C_4H_9(C_2H_5)N$	CCH_3	CCH_3	N	H	H	A	CH_3	---
920	CH	$C_4H_9(C_2H_5)N$	CCH_3	CCH_3	N	H	H	B	CH_3	---
921	CH	$C_4H_9(C_2H_5)N$	CCH_3	CCH_3	N	H	H	C	CH_3	---
922	CH	$C_4H_9(C_2H_5)N$	CCH_3	CCH_3	N	H	H	D	CH_3	---
923	CH	$C_4H_9(C_2H_5)N$	CCH_3	CCH_3	N	H	H	E	CH_3	---
924	CH	$C_4H_9(C_2H_5)N$	CCH_3	CCH_3	N	H	H	F	CH_3	---
925	CH	$C_4H_9(C_2H_5)N$	CCH_3	CCH_3	N	H	H	G	CH_3	---

926	CH	$C_4H_9(C_2H_5)N$	CCH_3	CCH_3	N	H	H	J	CH_3	---
927	CH	$(C_2H_5)_2N$	CCH_3	CCH_3	N	H	H	A	CH_3	---
928	CH	$(C_2H_5)_2N$	CCH_3	CCH_3	N	H	H	B	CH_3	---
929	CH	$(C_2H_5)_2N$	CCH_3	CCH_3	N	H	H	C	CH_3	---
930	CH	$(C_2H_5)_2N$	CCH_3	CCH_3	N	H	H	D	CH_3	---
931	CH	$(C_2H_5)_2N$	CCH_3	CCH_3	N	H	H	E	CH_3	---
932	CH	$(C_2H_5)_2N$	CCH_3	CCH_3	N	H	H	F	CH_3	---
933	CH	$(C_2H_5)_2N$	CCH_3	CCH_3	N	H	H	G	CH_3	---
934	CH	$(C_2H_5)_2N$	CCH_3	CCH_3	N	H	H	J	CH_3	---
935	CH	$CH_3OCH_2CH(C_2H_5)NH$	CCH_3	CCH_3	N	H	H	A	CH_3	---
936	CH	$CH_3OCH_2CH(C_2H_5)NH$	CCH_3	CCH_3	N	H	H	B	CH_3	---
937	CH	$CH_3OCH_2CH(C_2H_5)NH$	CCH_3	CCH_3	N	H	H	C	CH_3	---
938	CH	$CH_3OCH_2CH(C_2H_5)NH$	CCH_3	CCH_3	N	H	H	D	CH_3	---
939	CH	$CH_3OCH_2CH(C_2H_5)NH$	CCH_3	CCH_3	N	H	H	E	CH_3	---
940	CH	$CH_3OCH_2CH(C_2H_5)NH$	CCH_3	CCH_3	N	H	H	F	CH_3	---
941	CH	$CH_3OCH_2CH(C_2H_5)NH$	CCH_3	CCH_3	N	H	H	G	CH_3	---
942	CH	$CH_3OCH_2CH(C_2H_5)NH$	CCH_3	CCH_3	N	H	H	J	CH_3	---
943	CH	$[CH_3O(CH_2)_2]_2N$	CCH_3	CCH_3	N	H	H	A	CH_3	---
944	CH	$[CH_3O(CH_2)_2]_2N$	CCH_3	CCH_3	N	H	H	B	CH_3	---
945	CH	$[CH_3O(CH_2)_2]_2N$	CCH_3	CCH_3	N	H	H	C	CH_3	---
946	CH	$[CH_3O(CH_2)_2]_2N$	CCH_3	CCH_3	N	H	H	D	CH_3	---
947	CH	$[CH_3O(CH_2)_2]_2N$	CCH_3	CCH_3	N	H	H	E	CH_3	---
948	CH	$[CH_3O(CH_2)_2]_2N$	CCH_3	CCH_3	N	H	H	F	CH_3	---
949	CH	$[CH_3O(CH_2)_2]_2N$	CCH_3	CCH_3	N	H	H	G	CH_3	---
950	CH	$[CH_3O(CH_2)_2]_2N$	CCH_3	CCH_3	N	H	H	J	CH_3	---
951	CH	$(C_2H_5)_2CHNH$	CCH_3	CCH_3	N	H	H	A	CH_3	---
952	CH	$(C_2H_5)_2CHNH$	CCH_3	CCH_3	N	H	H	B	CH_3	---

953	CH	$(C_2H_5)_2CHNH$	CCH_3	CCH_3	N	H	H	C	CH_3	---
954	CH	$(C_2H_5)_2CHNH$	CCH_3	CCH_3	N	H	H	D	CH_3	---
955	CH	$(C_2H_5)_2CHNH$	CCH_3	CCH_3	N	H	H	E	CH_3	---
956	CH	$(C_2H_5)_2CHNH$	CCH_3	CCH_3	N	H	H	F	CH_3	---
957	CH	$(C_2H_5)_2CHNH$	CCH_3	CCH_3	N	H	H	G	CH_3	---
958	CH	$(C_2H_5)_2CHNH$	CCH_3	CCH_3	N	H	H	J	CH_3	---
959	N	$C_4H_9(C_2H_5)N$	N	N	N	CH_3	CH_3	A	CH_3	---
960	N	$C_4H_9(C_2H_5)N$	N	N	N	H	H	A	H	---
961	N	$C_4H_9(C_2H_5)N$	N	N	N	H	H	A	CN	---
962	N	$C_4H_9(C_2H_5)N$	CH	CH	N	CH_3	CH_3	A	CH_3	---
963	N	$C_4H_9(C_2H_5)N$	CH	CH	N	H	H	A	H	---
964	N	$C_4H_9(C_2H_5)N$	CH	CH	N	H	H	A	CN	---
965	N	$C_4H_9(C_2H_5)N$	CCH_3	CCH_3	N	CH_3	CH_3	A	CH_3	---
966	N	$C_4H_9(C_2H_5)N$	CCH_3	CCH_3	N	H	H	A	H	---
967	N	$C_4H_9(C_2H_5)N$	CCH_3	CCH_3	N	H	H	A	CN	---

Utility

CRF-R1 Receptor Binding Assay for the Evaluation of Biological Activity

The following is a description of the isolation of cell membranes containing cloned human CRF-R1 receptors for use in the standard binding assay as well as a description of the assay itself.

Messenger RNA was isolated from human hippocampus. The mRNA was reverse transcribed using oligo (dt) 12-18 and the coding region was amplified by PCR from start to stop codons The resulting PCR fragment was cloned into the EcoRV site of pGEMV, from whence the insert was reclaimed using XhoI + XbaI and cloned into the XhoI + XbaI sites of vector pm3ar (which contains a CMV promoter, the SV40 't' splice and early poly A signals, an Epstein-Barr viral origin of replication, and a hygromycin selectable marker). The resulting expression vector, called phchCRFR was transfected in 293EBNA cells and cells retaining the episome were selected in the presence of 400 µM hygromycin. Cells surviving 4 weeks of selection in hygromycin were pooled, adapted to growth in suspension and used to generate membranes for the binding assay described below. Individual aliquots containing approximately 1 x 10^8 of the suspended cells were then centrifuged to form a pellet and frozen.

For the binding assay a frozen pellet described above containing 293EBNA cells transfected with hCRFR1 receptors is homogenized in 10 ml of ice cold tissue buffer (50 mM HEPES buffer pH 7.0, containing 10 mM $MgCl_2$, 2 mM EGTA, 1 µg/l aprotinin, 1 µg/ml leupeptin and 1 µg/ml pepstatin). The homogenate is centrifuged at 40,000 x g for 12 min and the resulting pellet rehomogenized in 10 ml of tissue buffer. After another centrifugation at 40,000 x g for 12 min, the pellet is

resuspended to a protein concentration of 360 µg/ml to be used in the assay.

Binding assays are performed in 96 well plates; each well having a 300 µl capacity. To each well is added 50 µl of test drug dilutions (final concentration of drugs range from 10^{-10} - 10^{-5} M), 100 µl of ^{125}I-ovine-CRF (^{125}I-o-CRF) (final concentration 150 pM) and 150 µl of the cell homogenate described above. Plates are then allowed to incubate at room temperature for 2 hours before filtering the incubate over GF/F filters (presoaked with 0.3% polyethyleneimine) using an appropriate cell harvester. Filters are rinsed 2 times with ice cold assay buffer before removing individual filters and assessing them for radioactivity on a gamma counter.

Curves of the inhibition of ^{125}I-o-CRF binding to cell membranes at various dilutions of test drug are analyzed by the iterative curve fitting program LIGAND (P.J. Munson and D. Rodbard, *Anal. Biochem.* 107:220 (**1980**), which provides Ki values for inhibition which are then used to assess biological activity.

A compound is considered to be active if it has a K_i value of less than about 10000 nM for the inhibition of CRF.

Inhibition of CRF-Stimulated Adenylate Cyclase Activity

Inhibition of CRF-stimulated adenylate cyclase activity was performed as described by G. Battaglia et al. *Synapse* **1**:572 (**1987**). Briefly, assays were carried out at 37° C for 10 min in 200 ml of buffer containing 100 mM Tris-HCl (pH 7.4 at 37° C), 10 mM $MgCl_2$, 0.4 mM EGTA, 0.1% BSA, 1 mM isobutylmethylxanthine (IBMX), 250 units/ml phosphocreatine kinase, 5 mM creatine phosphate, 100 mM guanosine 5'-triphosphate, 100 nM oCRF, antagonist peptides (concentration range 10^{-9} to 10^{-6}m) and 0.8 mg original wet weight tissue (approximately 40-60 mg protein). Reactions were

initiated by the addition of 1 mM ATP/^{32}P]ATP (approximately 2-4 mCi/tube) and terminated by the addition of 100 ml of 50 mM Tris-HCL, 45 mM ATP and 2% sodium dodecyl sulfate. In order to monitor the recovery of cAMP, 1 µl of [^{3}H]cAMP (approximately 40,000 dpm) was added to each tube prior to separation. The separation of [^{32}P]cAMP from [^{32}P]ATP was performed by sequential elution over Dowex and alumina columns. Recovery was consistently greater than 80%.

Some compounds of this invention were tested in this assay and found to be active.

In vivo Biological Assay

The *in vivo* activity of the compounds of the present invention can be assessed using any one of the biological assays available and accepted within the art. Illustrative of these tests include the Acoustic Startle Assay, the Stair Climbing Test, and the Chronic Administration Assay. These and other models useful for the testing of compounds of the present invention have been outlined in C.W. Berridge and A.J. Dunn *Brain Research Reviews* 15:71 (**1990**)

Compounds may be tested in any species of rodent or small mammal. Disclosure of the assays herein is not intended to limit the enablement of the invention.

Compounds of this invention have utility in the treatment of inbalances associated with abnormal levels of corticotropin releasing factor in patients suffering from depression, affective disorders, and/or anxiety.

Compounds of this invention can be administered to treat these abnormalities by means that produce contact of the active agent with the agent's site of action in the body of a mammal. The compounds can be administered by any conventional means available for use in conjunction with pharmaceuticals either as individual therapeutic agent or in combination of therapeutic agents. They can be administered alone, but will

generally be administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

The dosage administered will vary depending on the use and known factors such as pharmacodynamic character of the particular agent, and its mode and route of administration; the recipient's age, weight, and health; nature and extent of symptoms; kind of concurrent treatment; frequency of treatment; and desired effect. For use in the treatment of said diseases or conditions, the compounds of this invention can be orally administered daily at a dosage of the active ingredient of 0.002 to 200 mg/kg of body weight. Ordinarily, a dose of 0.01 to 10 mg/kg in divided doses one to four times a day, or in sustained release formulation will be effective in obtaining the desired pharmacological effect.

Dosage forms (compositions) suitable for administration contain from about 1 mg to about 100 mg of active ingredient per unit. In these pharmaceutical compositions, the active ingredient will ordinarily be present in an amount of about 0.5 to 95% by weight based on the total weight of the composition.

The active ingredient can be administered orally is solid dosage forms, such as capsules, tablets and powders; or in liquid forms such as elixirs, syrups, and/or suspensions. The compounds of this invention can also be administered parenterally in sterile liquid dose formulations.

Gelatin capsules can be used to contain the active ingredient and a suitable carrier such as but not limited to lactose, starch, magnesium stearate, steric acid, or cellulose derivatives. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of medication over a period of time. Compressed tablets can be sugar-

coated or film-coated to mask any unpleasant taste, or used to protect the active ingredients from the atmosphere, or to allow selective disintegration of the tablet in the gastrointestinal tract.

Liquid dose forms for oral administration can contain coloring or flavoring agents to increase patient acceptance.

In general, water, pharmaceutically acceptable oils, saline, aqueous dextrose (glucose), and related sugar solutions and glycols, such as propylene glycol or polyethylene glycol, are suitable carriers for parenteral solutions. Solutions for parenteral administration preferably contain a water soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, butter substances. Antioxidizing agents, such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or in combination, are suitable stabilizing agents. Also used are citric acid and its salts, and EDTA. In addition, parenteral solutions can contain preservatives such as benzalkonium chloride, methyl- or propyl-paraben, and chlorobutanol.

Suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences", A. Osol, a standard reference in the field.

Useful pharmaceutical dosage-forms for administration of the compounds of this invention can be illustrated as follows:

Capsules

A large number of units capsules are prepared by filling standard two-piece hard gelatin capsules each with 100 mg of powdered active ingredient, 150 mg lactose, 50 mg cellulose, and 6 mg magnesium stearate.

Soft Gelatin Capsules

A mixture of active ingredient in a digestible oil such as soybean, cottonseed oil, or olive oil is

prepared and injected by means of a positive displacement was pumped into gelatin to form soft gelatin capsules containing 100 mg of the active ingredient. The capsules were washed and dried.

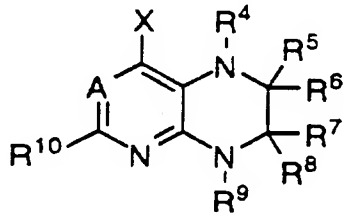
Tablets

A large number of tablets are prepared by conventional procedures so that the dosage unit was 100 mg active ingredient, 0.2 mg of colloidal silicon dioxide, 5 mg of magnesium stearate, 275 mg of microcrystalline cellulose, 11 mg of starch, and 98.8 mg lactose. Appropriate coatings may be applied to increase palatability or delayed adsorption.

The compounds of this invention may also be used as reagents or standards in the biochemical study of neurological function, dysfunction, and disease.

Claims:

1. A method of treating an affective disorder, anxiety, depression, irritable bowel syndrome, post-traumatic stress disorder, supranuclear palsy, immune suppression, Alzheimer's disease, gastrointestinal disease, anorexia nervosa or other feeding disorder, drug or alcohol withdrawal symptoms, drug addiction, or inflammatory disorder in a mammal comprising administering to the mammal a therapeutically effective amount of a CRF antagonist compound of formula I:



(I)

or a pharmaceutically accetable salt or prodrug thereof, wherein:

A is N or C-R^{11};

X is H, OR^1, $S(O)_nR^1$, NR^1R^2, $CR^1R^2R^3$, phenyl (optionally substituted with 1-4 groups independently chosen from halogen, C_1-C_4 haloalkyl, nitro, C_1-C_4 alkyl, C_2-C_5 carboalkoxy, cyano, OH, C_1-C_4 alkoxy, SH, C_1-C_4 alkylthio, NH_2, C_1-C_4 alkylamino, C_2-C_8 dialkylamino, or phenyl) or heteroaryl (optionally substituted at one to all valence-allowed positions with groups independently chosen from halogen, C_1-C_4 haloalkyl, nitro, C_1-C_4 alkyl, C_2-C_5 carboalkoxy, cyano, OH, C_1-C_4 alkoxy, SH, C_1-C_4 alkylthio, NH_2, C_1-C_4 alkylamino, C_2-C_8 dialkylamino, or phenyl);

n is 0, 1 or 2;

R^1 is C_1-C_{12} alkyl, C_2-C_{12} alkoxyalkyl, C_3-C_{12} cycloalkyl, C_4-C_{12} cycloalkylalkyl, C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, aryl-(C_1-C_{12} alkyl), C_3-C_{12}

dialkylaminoalkyl, C_2-C_{13} cyanoalkyl, C_2-C_5 carboalkoxy-(C_1-C_{12} alkyl), phenyl (optionally substituted with 1-4 groups independently chosen from halogen, C_1-C_4 haloalkyl, nitro, C_1-C_4 alkyl, C_2-C_5 carboalkoxy, cyano, OH, C_1-C_4 alkoxy, SH, C_1-C_4 alkylthio, NH_2, C_1-C_4 alkylamino, C_2-C_8 dialkylamino, or phenyl), or heteroaryl (optionally substituted at one to all valence-allowed positions with groups independently chosen from halogen, C_1-C_4 haloalkyl, nitro, C_1-C_4 alkyl, C_2-C_5 carboalkoxy, cyano, OH, C_1-C_4 alkoxy, SH, C_1-C_4 alkylthio, NH_2, C_1-C_4 alkylamino, C_2-C_8 dialkylamino, or phenyl);

R^2 and R^3 are independently chosen from H, C_1-C_{12} alkyl, C_2-C_{12} alkoxyalkyl, C_3-C_{12} cycloalkyl, C_4-C_{12} cycloalkylalkyl, C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, aryl-(C_1-C_{12} alkyl), C_3-C_{12} dialkylaminoalkyl, C_2-C_{13} cyanoalkyl, C_1-C_4 carboalkoxy, C_2-C_{12} carboalkoxyalkyl, $C(=O)CH_3$, phenyl (optionally substituted with 1-4 groups independently chosen from halogen, C_1-C_4 haloalkyl, nitro, C_1-C_4 alkyl, C_2-C_5 carboalkoxy, cyano, OH, C_1-C_4 alkoxy, SH, C_1-C_4 alkylthio, NH_2, C_1-C_4 alkylamino, C_2-C_8 dialkylamino, or phenyl), or heteroaryl (optionally substituted at one to all valence-allowed positions with groups independently chosen from halogen, C_1-C_4 haloalkyl, nitro, C_1-C_4 alkyl, C_2-C_5 carboalkoxy, cyano, OH, C_1-C_4 alkoxy, SH, C_1-C_4 alkylthio, NH_2, C_1-C_4 alkylamino, C_2-C_8 dialkylamino, or phenyl);

R^4 is H, C_1-C_{12} alkyl, allyl, propargyl or benzyl (optionally substituted with 1-4 groups independently chosen from halogen, C_1-C_4 haloalkyl, nitro, C_1-C_4 alkyl, C_2-C_5 carboalkoxy, cyano, OH, C_1-C_4 alkoxy, SH, C_1-C_4 alkylthio, NH_2, C_1-C_4 alkylamino, C_2-C_8 dialkylamino, or phenyl);

R^1 and R^4 may also optionally be taken together, along with the other four interconnected atoms, to form a ring of 5-9 total atoms, the structural sequence

between the X group and the ring nitrogen atom consisting of the group $(CH_2)_pW(CH_2)_q$;

p and q are independently 0, 1 or 2;

W is CH_2, $C(CH_3)_2$, C(=O), O, S or NCH_3;

R^5, R^6, R^7 and R^8 are independently chosen from H, C_1-C_4 alkyl, allyl, propargyl, phenyl (optionally substituted with 1-4 groups independently chosen from halogen, C_1-C_4 haloalkyl, nitro, C_1-C_4 alkyl, C_2-C_5 carboalkoxy, cyano, OH, C_1-C_4 alkoxy, SH, C_1-C_4 alkylthio, NH_2, C_1-C_4 alkylamino, C_2-C_8 dialkylamino, or phenyl) or benzyl (optionally substituted with 1-4 groups independently chosen from halogen, C_1-C_4 haloalkyl, nitro, C_1-C_4 alkyl, C_2-C_5 carboalkoxy, cyano, OH, C_1-C_4 alkoxy, SH, C_1-C_4 alkylthio, NH_2, C_1-C_4 alkylamino, C_2-C_8 dialkylamino, or phenyl);

R^4, R^5 and R^6 may also be taken together, along with the two interconnecting atoms, to constitute either an imidazole or tetrazole ring, the imidazole ring being optionally substituted with 1-2 groups chosen independently from C_1-C_4 alkyl or phenyl;

R^5 and R^6 may also be taken together to be O, S or NR^{12};

R^9 is phenyl (optionally substituted with 1-4 groups chosen from halogen, C_1-C_4 haloalkyl, C_1-C_4 alkyl, C_2-C_6 alkenyl, C_1-C_4 alkoxy, C_1-C_4 alkylthio, C_1-C_4 alkylsulfonyl, C_2-C_6 dialkylamino, nitro, C_2-C_5 carboalkoxy or cyano), pyridyl (optionally substituted with 1-4 groups chosen from halogen, C_1-C_4 haloalkyl, C_1-C_4 alkyl, C_2-C_6 alkenyl, C_1-C_4 alkoxy, C_1-C_4 alkylthio, C_1-C_4 alkylsulfonyl, C_2-C_6 dialkylamino, nitro, C_2-C_5 carboalkoxy or cyano), or pyrimidyl (optionally substituted with 1-4 groups chosen from halogen, C_1-C_4 haloalkyl, C_1-C_4 alkyl, C_2-C_6 alkenyl, C_1-C_4 alkoxy, C_1-C_4 alkylthio, C_1-C_4 alkylsulfonyl, C_2-C_6 dialkylamino, nitro, C_2-C_5 carboalkoxy or cyano);

R^{10} is H, C_1-C_4 alkyl or cyano;
R^{11} is H, C_1-C_4 alkyl or halogen;
R^{12} is H, C_1-C_4 alkyl or phenyl;
aryl is phenyl, biphenyl or naphthyl; and
heteroaryl is pyridyl, pyrimidinyl, triazinyl, furanyl, quinolinyl, isoquinolinyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrrolyl, oxazolyl, benzofuranyl, benzothienyl, benzthiazolyl, isoxazolyl or pyrazolyl.

2. Method of claim 1 wherein, in the compound of formula I,
X is OR^1, NR^1R^2, $CR^1R^2R^3$, or phenyl (optionally substituted at the 2-position with CF_3, nitro, halogen or cyano);
R^1 is C_1-C_{12} alkyl , C_2-C_{12} alkoxyalkyl, C_3-C_{12} cycloalkyl, C_4-C_{12} cycloalkylalkyl, aryl-(C_1-C_{12} alkyl), C_3-C_{12} dialkylaminoalkyl, or phenyl (optionally substituted with 1-4 groups independently chosen from halogen, haloalkyl, nitro, C_1-C_4 alkyl, C_2-C_5 carboalkoxy, cyano, OH, C_1-C_4 alkoxy, SH, C_1-C_4 alkylthio, NH_2, C_1-C_4 alkylamino, C_2-C_8 dialkylamino, or phenyl);
R^4 is H or C_1-C_4 alkyl;
R^5 and R^6 are either H or C_1-C_4 alkyl;
R^4, R^5 and R^6 may also be taken together, along with the two interconnecting atoms, to constitute a tetrazole ring;
R^9 is phenyl (optionally substituted with 1-4 groups chosen from halogen, C_1-C_4 haloalkyl, C_1-C_4 alkyl, C_2-C_6 alkenyl, C_1-C_4 alkoxy, C_1-C_4 alkylthio, C_1-C_4 alkylsulfonyl, C_2-C_6 dialkylamino, nitro, C_2-C_5 carboalkoxy or cyano), 3-pyridyl (optionally substituted with 1-4 groups chosen from halogen, C_1-C_4 haloalkyl, C_1-C_4 alkyl, C_2-C_6 alkenyl, C_1-C_4 alkoxy, C_1-C_4 alkylthio, C_1-C_4 alkylsulfonyl, C_2-C_6 dialkylamino, nitro, C_2-C_5 carboalkoxy or cyano),

or 5-pyrimidyl (optionally substituted with 1-4 groups chosen from halogen, C_1-C_4 haloalkyl, C_1-C_4 alkyl, C_2-C_6 alkenyl, C_1-C_4 alkoxy, C_1-C_4 alkylthio, C_1-C_4 alkylsulfonyl, C_2-C_6 dialkylamino, nitro, C_2-C_5 carboalkoxy or cyano);

R^{10} is CH_3;

and R^{11} is H.

3. Method of claim 2 wherein, in the compound of formula (I):

A is N;

X is NR^1R^2 or $CR^1R^2R^3$;

R^1 is C_1-C_6 alkyl or C_2-C_8 alkoxyalkyl;

R^2 and R^3 are independently H, C_1-C_6 alkyl or C_2-C_8 alkoxyalkyl;

R^4 is H;

R^5 and R^6 are H;

R^7 and R^8 are independently H or CH_3; and

R^9 is phenyl (optionally substituted with 1-4 groups chosen from halogen, C_1-C_4 haloalkyl, C_1-C_4 alkyl, C_2-C_6 alkenyl, C_1-C_4 alkoxy, C_1-C_4 alkylthio, C_1-C_4 alkylsulfonyl, C_2-C_6 dialkylamino, nitro, C_2-C_5 carboalkoxy or cyano).

4. Method of claim 1 wherein the compound of formula I is selected from:

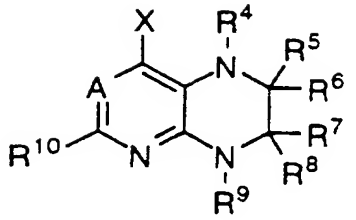
8-(2-bromo-4-isopropylphenyl)-4-(ethylbutylamino)-2-methyl-5,6,7,8-tetrahydropteridine;

8-(2-chloro-4,6-dimethoxyphenyl)-4-(ethylbutylamino)-2-methyl-5,6,7,8-tetrahydropteridine;

4-(ethylbutylamino)-2-methyl-8-(2,4,6-trimethylphenyl)-5,6,7,8-tetrahydropteridine; and

4-(1-methoxy-2-butyl)amino-2-methyl-8-(2,4,6-trimethylphenyl)-5,6,7,8-tetrahydropteridine.

5. A CRF antagonist compound of formula I:



(I)

or a pharmaceutically accetable salt or prodrug thereof, wherein:

A is N or C-R^{11};

X is H, OR^1, $S(O)_nR^1$, NR^1R^2, $CR^1R^2R^3$, phenyl (optionally substituted with 1-4 groups independently chosen from halogen, C_1-C_4 haloalkyl, nitro, C_1-C_4 alkyl, C_2-C_5 carboalkoxy, cyano, OH, C_1-C_4 alkoxy, SH, C_1-C_4 alkylthio, NH_2, C_1-C_4 alkylamino, C_2-C_8 dialkylamino, or phenyl) or heteroaryl (optionally substituted at one to all valence-allowed positions with groups independently chosen from halogen, C_1-C_4 haloalkyl, nitro, C_1-C_4 alkyl, C_2-C_5 carboalkoxy, cyano, OH, C_1-C_4 alkoxy, SH, C_1-C_4 alkylthio, NH_2, C_1-C_4 alkylamino, C_2-C_8 dialkylamino, or phenyl);

n is 0, 1 or 2;

R^1 is C_1-C_{12} alkyl, C_2-C_{12} alkoxyalkyl, C_3-C_{12} cycloalkyl, C_4-C_{12} cycloalkylalkyl, C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, aryl-(C_1-C_{12} alkyl), C_3-C_{12} dialkylaminoalkyl, C_2-C_{13} cyanoalkyl, C_2-C_5 carboalkoxy-(C_1-C_{12} alkyl), phenyl (optionally substituted with 1-4 groups independently chosen from halogen, C_1-C_4 haloalkyl, nitro, C_1-C_4 alkyl, C_2-C_5 carboalkoxy, cyano, OH, C_1-C_4 alkoxy, SH, C_1-C_4 alkylthio, NH_2, C_1-C_4 alkylamino, C_2-C_8 dialkylamino, or phenyl), or heteroaryl (optionally substituted at one to all valence-allowed positions with groups independently chosen from halogen, C_1-C_4 haloalkyl, nitro, C_1-C_4 alkyl, C_2-C_5 carboalkoxy, cyano, OH, C_1-C_4 alkoxy, SH, C_1-C_4 alkylthio, NH_2, C_1-C_4 alkylamino, C_2-C_8 dialkylamino, or phenyl);

R^2 and R^3 are independently chosen from H, C_1-C_{12} alkyl, C_2-C_{12} alkoxyalkyl, C_3-C_{12} cycloalkyl, C_4-C_{12} cycloalkylalkyl, C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, aryl-(C_1-C_{12} alkyl), C_3-C_{12} dialkylaminoalkyl, C_2-C_{13} cyanoalkyl, C_1-C_4 carboalkoxy, C_2-C_{12} carboalkoxyalkyl, $C(=O)CH_3$, phenyl (optionally substituted with 1-4 groups independently chosen from halogen, C_1-C_4 haloalkyl, nitro, C_1-C_4 alkyl, C_2-C_5 carboalkoxy, cyano, OH, C_1-C_4 alkoxy, SH, C_1-C_4 alkylthio, NH_2, C_1-C_4 alkylamino, C_2-C_8 dialkylamino, or phenyl), or heteroaryl (optionally substituted at one to all valence-allowed positions with groups independently chosen from halogen, C_1-C_4 haloalkyl, nitro, C_1-C_4 alkyl, C_2-C_5 carboalkoxy, cyano, OH, C_1-C_4 alkoxy, SH, C_1-C_4 alkylthio, NH_2, C_1-C_4 alkylamino, C_2-C_8 dialkylamino, or phenyl);

R^4 is H, C_1-C_{12} alkyl, allyl, propargyl or benzyl (optionally substituted with 1-4 groups independently chosen from halogen, C_1-C_4 haloalkyl, nitro, C_1-C_4 alkyl, C_2-C_5 carboalkoxy, cyano, OH, C_1-C_4 alkoxy, SH, C_1-C_4 alkylthio, NH_2, C_1-C_4 alkylamino, C_2-C_8 dialkylamino, or phenyl);

R^1 and R^4 may also optionally be taken together, along with the other four interconnected atoms, to form a ring of 5-9 total atoms, the structural sequence between the X group and the ring nitrogen atom consisting of the group $(CH_2)_pW(CH_2)_q$;

p and q are independently 0, 1 or 2;

W is CH_2, $C(CH_3)_2$, $C(=O)$, O, S or NCH_3;

R^5, R^6, R^7 and R^8 are independently chosen from H, C_1-C_4 alkyl, allyl, propargyl, phenyl (optionally substituted with 1-4 groups independently chosen from halogen, C_1-C_4 haloalkyl, nitro, C_1-C_4 alkyl, C_2-C_5 carboalkoxy, cyano, OH, C_1-C_4 alkoxy, SH, C_1-C_4 alkylthio, NH_2, C_1-C_4 alkylamino, C_2-C_8 dialkylamino, or phenyl) or benzyl (optionally substituted with 1-4 groups independently chosen

from halogen, C_1-C_4 haloalkyl, nitro, C_1-C_4 alkyl, C_2-C_5 carboalkoxy, cyano, OH, C_1-C_4 alkoxy, SH, C_1-C_4 alkylthio, NH_2, C_1-C_4 alkylamino, C_2-C_8 dialkylamino, or phenyl);

R^4, R^5 and R^6 may also be taken together, along with the two interconnecting atoms, to constitute either an imidazole or tetrazole ring, the imidazole ring being optionally substituted with 1-2 groups chosen independently from C_1-C_4 alkyl or phenyl;

R^9 is phenyl (optionally substituted with 1-4 groups chosen from halogen, C_1-C_4 haloalkyl, C_1-C_4 alkyl, C_2-C_6 alkenyl, C_1-C_4 alkoxy, C_1-C_4 alkylthio, C_1-C_4 alkylsulfonyl, C_2-C_6 dialkylamino, nitro, C_2-C_5 carboalkoxy or cyano), pyridyl (optionally substituted with 1-4 groups chosen from halogen, C_1-C_4 haloalkyl, C_1-C_4 alkyl, C_2-C_6 alkenyl, C_1-C_4 alkoxy, C_1-C_4 alkylthio, C_1-C_4 alkylsulfonyl, C_2-C_6 dialkylamino, nitro, C_2-C_5 carboalkoxy or cyano), or pyrimidyl (optionally substituted with 1-4 groups chosen from halogen, C_1-C_4 haloalkyl, C_1-C_4 alkyl, C_2-C_6 alkenyl, C_1-C_4 alkoxy, C_1-C_4 alkylthio, C_1-C_4 alkylsulfonyl, C_2-C_6 dialkylamino, nitro, C_2-C_5 carboalkoxy or cyano);

R^{10} is H, C_1-C_4 alkyl or cyano;

R^{11} is H, C_1-C_4 alkyl or halogen;

R^{12} is H, C_1-C_4 alkyl or phenyl;

aryl is phenyl, biphenyl or naphthyl; and

heteroaryl is pyridyl, pyrimidinyl, triazinyl, furanyl, quinolinyl, isoquinolinyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrrolyl, oxazolyl, benzofuranyl, benzothienyl, benzthiazolyl, isoxazolyl or pyrazolyl.

6. A compound of claim 5 wherein:

X is OR^1, NR^1R^2, $CR^1R^2R^3$, or phenyl (optionally

substituted at the 2-position with CF_3, nitro, halogen or cyano);

R^1 is C_1-C_{12} alkyl , C_2-C_{12} alkoxyalkyl, C_3-C_{12} cycloalkyl, C_4-C_{12} cycloalkylalkyl, aryl-(C_1-C_{12} alkyl), C_3-C_{12} dialkylaminoalkyl, or phenyl (optionally substituted with 1-4 groups independently chosen from halogen, haloalkyl, nitro, C_1-C_4 alkyl, C_2-C_5 carboalkoxy, cyano, OH, C_1-C_4 alkoxy, SH, C_1-C_4 alkylthio, NH_2, C_1-C_4 alkylamino, C_2-C_8 dialkylamino, or phenyl);

R^4 is H or C_1-C_4 alkyl;

R^5 and R^6 are either H or C_1-C_4 alkyl;

R^4, R^5 and R^6 may also be taken together, along with the two interconnecting atoms, to constitute a tetrazole ring;

R^9 is phenyl (optionally substituted with 1-4 groups chosen from halogen, C_1-C_4 haloalkyl, C_1-C_4 alkyl, C_2-C_6 alkenyl, C_1-C_4 alkoxy, C_1-C_4 alkylthio, C_1-C_4 alkylsulfonyl, C_2-C_6 dialkylamino, nitro, C_2-C_5 carboalkoxy or cyano), 3-pyridyl (optionally substituted with 1-4 groups chosen from halogen, C_1-C_4 haloalkyl, C_1-C_4 alkyl, C_2-C_6 alkenyl, C_1-C_4 alkoxy, C_1-C_4 alkylthio, C_1-C_4 alkylsulfonyl, C_2-C_6 dialkylamino, nitro, C_2-C_5 carboalkoxy or cyano), or 5-pyrimidyl (optionally substituted with 1-4 groups chosen from halogen, C_1-C_4 haloalkyl, C_1-C_4 alkyl, C_2-C_6 alkenyl, C_1-C_4 alkoxy, C_1-C_4 alkylthio, C_1-C_4 alkylsulfonyl, C_2-C_6 dialkylamino, nitro, C_2-C_5 carboalkoxy or cyano);

R^{10} is CH_3;

and R^{11} is H.

7. A compound of claim 6 wherein:

A is N;

X is NR^1R^2 or $CR^1R^2R^3$;

R^1 is C_1-C_6 alkyl or C_2-C_8 alkoxyalkyl;

R^2 and R^3 are independently H, C_1-C_6 alkyl or C_2-C_8 alkoxyalkyl;
R^4 is H;
R^5 and R^6 are H;
R^7 and R^8 are independently H or CH_3; and
R^9 is phenyl (optionally substituted with 1-4 groups chosen from halogen, C_1-C_4 haloalkyl, C_1-C_4 alkyl, C_2-C_6 alkenyl, C_1-C_4 alkoxy, C_1-C_4 alkylthio, C_1-C_4 alkylsulfonyl, C_2-C_6 dialkylamino, nitro, C_2-C_5 carboalkoxy or cyano).

8. A compound of claim 7 selected from:

8-(2-bromo-4-isopropylphenyl)-4-(ethylbutylamino)-2-methyl-5,6,7,8-tetrahydropteridine;
8-(2-chloro-4,6-dimethoxyphenyl)-4-(ethylbutylamino)-2-methyl-5,6,7,8-tetrahydropteridine;
4-(ethylbutylamino)-2-methyl-8-(2,4,6-trimethylphenyl)-5,6,7,8-tetrahydropteridine; and
4-(1-methoxy-2-butyl)amino-2-methyl-8-(2,4,6-trimethylphenyl)-5,6,7,8-tetrahydropteridine.

9. A composition comprising a therapeutically effective amount of compound of claim 5 and a pharmaceutically suitable carrier.

10. A composition comprising a therapeutically effective amount of compound of claim 6 and a pharmaceutically suitable carrier.

11. A composition comprising a therapeutically effective amount of compound of claim 7 and a pharmaceutically suitable carrier.

12. A composition comprising a therapeutically effective amount of compound of claim 8 and a pharmaceutically suitable carrier.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/08448

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) :A61K 31/495, 31/505; C07D 487/06, 487/16
US CL :514/249; 544/251, 256, 350
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 514/249; 544/258, 260, 251, 256

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS ONLINE STRUCTURE SEARCH

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X - Y	US 5,198,547 A (BAILEY et al.) 30 March 1993, see column 7 structure IX and column 2 lines 64 to column 3 line 14.	5, 6, 9, 10 ----------1, 2
A	US 4,665,182 A (NICHOL et al.) 12 May 1987, see claim 1	1-12
A	US 4,701,455 A (NICHOL et al.) 20 October 1987, see claim 1.	1-12
A	US 4,091,219 A (DENZEL et al.) 23 May 1978, see Table, columns 5 to 8.	1-12
X	US 4,510,141 A (HECKENDORN) 09 April 1985, see column 20 line 34 to column 25 line 8 and Abstract Penultimate line.	1, 2, 5, 6, 9, 10

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 AUGUST 1997	09 SEP 1997
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer D. G. DAUS Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/08448

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JP 08-092250 (A. SAHI BREWERIES) 09 April 1996, see page 2, column 1 structure (3) and column 2, structure (1).	1-12

Form PCT/ISA/210 (continuation of second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/08448

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

I. Claims 1-2, (in part) 3, 4 to various disease treatments using III (A is N)
II. Claims 1-2 (in part) to various disease treatments using IV (a is CH)
III. Claims 5, 6, 9, 10 (in part) and 7, 8, 11, 12 to tetrahydropteridine (A is N)
IV. Claims 5, 6, 9, 10 (in part) to pyridopiperzines (A is CH).

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☒ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.